Coal Fly Ash:

General Causation Analyses

and Relevant Medical and Scientific Literature

Paul D. Terry, PhD, MPH, FACE

Testifying Expert

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INTRODUCTION

I am an epidemiologist and Fellow of the American College of Epidemiology. My current position is an Associate Professor in the University of Tennessee Department of Medicine, Graduate School of Medicine in Knoxville, Tennessee. I also have joint appointments as an Associate Professor with the Affiliate Faculty of the Institute of Biomedical Engineering, University of Tennessee and with the Comparative and Experimental Medicine Graduate Program, University of Tennessee. I was previously employed a Research Fellow with the National Institute of Environmental Health Sciences, Research Triangle Park, NC, and as a Biostatistician in the Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY. I have a B.A. from the State University of New York, a Masters in Public Health from the Department of Community Medicine and Health Care, University of Connecticut Health Center, Farmington, CT, a Med. dr. degree (equivalent to a Ph.D.) from the Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden, and a Ph.D. in Epidemiology from the Department of Epidemiology, Columbia University School of Public Health, Columbia-Presbyterian Medical Center, New York City, NY. I have practiced as an epidemiologist for over 15 years and have published over 120 articles and book chapters concerning epidemiological studies in the peer-reviewed literature. My current C.V. is attached as an exhibit to this Report with a list of my publications.

This report supplements my two previous reports of July 2017 and October 2017. In these previous reports I discussed the epidemiologic study that I had embarked upon to estimate the associations between exposure to coal ash and specific diseases, such as cancer, heart disease and respiratory illness, among workers engaged in the Kingston coal ash cleanup efforts, including the plaintiffs in this case. I developed a questionnaire to be administered to both exposed coal ash cleanup workers and a set of controls who were employed in the same industry. At that time, I was not a paid consultant, nor did I have a budget to do this work, so I relied upon the attorneys and their staff to assist in data collection. I was provided with responses by plaintiffs' attorneys for the exposed group who were plaintiffs in these cases, but the attorneys were not able to secure sufficient responses from controls who were not exposed in a timely manner. As a result, I have terminated the epidemiologic study that I originally planned to complete.

In my first supplemental report, relying upon a review of the questionnaire data for exposed plaintiffs, I provided a preliminary opinion that there appeared to me to be an excess burden of certain diseases among the coal ash workers, given the reported incidence rates of those same diseases in the general population, which I used for comparison. I also briefly reviewed some of the epidemiologic literature associated exposure to coal ash and its constituents, including fine particulates, with certain diseases seen in the exposed plaintiff group.

In March 2018 I was requested by plaintiffs' attorneys to conduct a far more thorough general causation analysis of the published epidemiologic literature regarding illnesses and physical conditions associated with exposure to coal ash. This general causation analysis is presented in this second Supplemental Report.

I have not testified as an expert witness within the past four (4) years. I am being compensated at a rate of $350 per hour for my time in this case.

Paul D. Terry, Ph.D., MPH, FACE

Methodology for General Causation Analysis

A general causation analysis answers the question "Can exposure to a chemical or other factor cause a disease?" To answer this question, a general causation analysis involves the following three steps:

1. Conducting a search of the relevant medical and scientific literature to identify journal articles and other documents, focusing primarily on observational epidemiological studies on human populations exposed to the chemical or other factor (such as cohort studies, case-control studies, case-crossover studies, and ecological studies)

2. Systemically reviewing reports of epidemiological studies and other information in journal articles and other documents that have been identified (including Methods, Results (including tests of statistical significance), Discussion (including consideration of alternative explanations of findings), and Conclusion sections of published reports

3. Applying established guidelines, such as the Bradford Hill Principles (also known as the "Bradford Hill Perspectives" and the "Bradford Hill Criteria") to the body of relevant medical and scientific literature. The nine Bradford Hill Principles are:

    a. Strength of association
    b. Consistency (replication) of findings among studies
    c. Temporality (temporal relationship)
    d. Biological gradient (dose-response relationship)
    e. Biological plausibility
    f. Specificity of association
    g. Coherence (with existing knowledge)
    h. Experiment (cessation of exposure)
    i. Analogy (reasoning by analogy)

The Bradford Hill principles are not meant to be used as a "causality checklist" because true causal associations don't necessarily have to be "strong," for example, or specific to one exposure or outcome. Rather, they are guides to assessing causality, with perhaps the first five ("a" through "e") being the most commonly used. (Reference: Hill AB. The Environment and Disease: Association or Causation? Proceedings of the Royal Society of Medicine 1965; 58: 295-300.)

General causation is distinct from specific causation, which answers the question "Did a specific exposure to a chemical or other factor cause a specific disease in a specific individual?" A specific causation analysis, but not a general causation analysis, takes into consideration the nature, levels, and duration of exposure of a specific individual to a specific chemical or other factor. A specific causation analysis also considers exposures that a specific individual has had to multiple chemicals or other factors, which may have exerted additive or synergistic (greater than additive) effects.

Methodology Used in This Report

This report applied the established methodology described above for determining general causation to address the questions of whether or not the following specific components of coal fly ash reported as being present in the coal ash at Kingston are causally associated with specific diseases reported among plaintiffs:

1. Fine particulate matter (particles having an aerodynamic diameter of 2.5 μ (microns) or less
2. Arsenic
3. Cadmium
4. Chromium
5. Lead
6. Nickel
7. Vanadium
8. Naturally occurring radioactive material (and ionizing radiation, in general)

For some diseases, such as allergic contact dermatitis (skin allergy), there are few relevant epidemiologic studies. However, as reflected in review articles and/or authoritative medical and government documents, specific chemicals have been established as causes of this disease.

Summary of Findings

As reflected in the remainder of this report, a number of the diseases found among one or more plaintiffs were determined by general causation analyses to be causally associated with one or more of these components of coal fly ash – that is, these components of coal fly ash can cause these diseases. The general causation associations found were as follows. The data and analyses supporting these general causation associations are detailed in the remainder of this report:

1. Lead in coal ash can cause hypertension.
2. Arsenic, cadmium, and fine particulate matter in coal ash can cause coronary artery disease.
3. Arsenic, cadmium, chromium, and fine particulate matter in coal ash can cause lung cancer.
4. Ionizing radiation in coal ash can cause leukemia.
5. Arsenic in coal ash can cause non-melanoma skin cancer.
6. Chromium and nickel in coal ash can cause allergic contact dermatitis (skin allergy).
7. Arsenic and lead in coal ash can cause peripheral neuropathy.
8. Chromium, fine particulate matter, nickel, and vanadium in coal ash can cause asthma.
9. Cadmium and fine particulate matter in coal ash can cause chronic obstructive pulmonary disease.

10. Fine particulate matter and other coal ash constituents can cause respiratory conditions, including cough, sore throat, dyspnea on exertion, chest pain or discomfort, bronchitis and emphysema.

Not shown in this report are additional general causation analyses performed regarding which causal associations were not found, such as for melanoma and for colorectal cancer.

Definitions of Epidemiologic Study Designs Cited and Discussed Below

Systematic review
A type of literature reviews that collect and critically analyzes multiple research studies or papers, using methods that are selected before one or more research questions are formulated, and then finding and analyzing studies that relate to and answer those questions in a structured methodology.

Meta-analysis
A quantitative, formal, epidemiological study used to systematically assess previous research studies to derive conclusions about that body of research.

Prospective Cohort Study
A study design where one or more groups of people are categorized in terms of one or more characteristics or exposures of interest, and then followed prospectively with respect to a disease or outcome. The outcomes from participants in each group is measured and relationships with specific characteristics or exposures determined.

Case-Control Study
A study that compares persons who have a disease or outcome of interest (cases) with persons who do not have the disease or outcome (controls) and looks back retrospectively to compare how frequently the exposure to a risk factor is present in each group to determine the relationship between the risk factor and the disease.

Cross-Sectional Study
A study that analyzes data from a population, or a representative subset, at a specific point in time (a "slice" of time).

Ecological Study
A study that analyzes data at the population or group level, rather than individual level (for example, a study that compares lung cancer mortality rates in each state with per capita tobacco sales in each state).

Case Report
A detailed report of the symptoms, medical and exposure histories, signs, diagnosis, treatment, and follow-up of an individuals.

Lead and Hypertension

Analysis of the following medical and scientific literature supports a causal association between exposure to lead in coal ash and occurrence of hypertension, based on satisfaction of the following Bradford Hill Principles:

Consistency
Temporality
Biologic Gradient (Dose-response Relationship)
Biologic Plausibility

A positive association between lead and hypertension has been observed in many epidemiologic studies over several decades among studies of different populations using several study designs, and controlling for a wide range of potentially confounding factors. In the cohort studies, exposure was measured prior to the measurement of the outcome (temporality), thus avoiding recall bias. Studies often showed positive dose-response associations between lead exposure level and blood pressure. The pathophysiology of lead-induced hypertension has been examined in several studies, and the association appears to be biologically plausible. Based on ample published literature, several meta-analyses have been performed concluding that there is an association between lead and hypertension. Whereas relative risk estimates have not always been very strong, per se, in several studies, relatively low levels of lead exposure were still associated with moderate (30% - 50%) estimates of increased risk.

Cohort Studies

Cheng Y, Schwartz J, Sparrow D, et al. Bone lead and blood lead levels in relation to baseline blood pressure and the prospective development of hypertension: The Normative Aging Study. American Journal of Epidemiology 2001; 153: 164-171.

This paper reported on a cohort analysis of 833 participants in the Normative Aging Study, a long-term cohort study. Among 519 individuals with no history of definite hypertension at the start of the study, cross-sectional analyses demonstrated a positive association between bone lead levels and systolic blood pressure. In addition, the study found that baseline bone lead levels were positively associated with the incidence of hypertension. The authors concluded that their findings support the hypothesis that cumulative exposure to lead, even at low levels sustained by the general population, may increase the risk of hypertension.

Glen B, Stewart W, Links J, et al. The longitudinal association of lead with blood pressure. Epidemiology 2003;14:30-36.

In this cohort study, lead, measured in blood and tibia, led to changes in blood pressure among 496 employees of a chemical-manufacturing facility who had occupational exposure to inorganic and organic lead. Cohort members provided three or four blood pressure measurements during the study. Blood lead at baseline averaged 4.6 microg/dL (standard deviation [SD] = 2.6) or 0.22 micromole/Liter (SD = 0.13).

Tibia lead at year three averaged 14.7-microg/gm (SD = 9.4) bone mineral. Change in systolic blood pressure during the study was associated with lead dose, with an average annual increase of 0.64 mmHg (standard error [SE] = 0.25), 0.73 mmHg (SE = 0.26), and 0.61 mmHg (SE = 0.27) for every standard deviation increase in blood lead at baseline, tibia lead at year three, or peak past tibia lead, respectively.

Cross-sectional Studies

Schwartz J. Lead, blood pressure, and cardiovascular disease in men and women. Environmental Health Perspectives 1991; 91: 71-75.

This paper reported on analyses of data from the Second National Health and Nutrition Examination Survey (1976-1980). It reported that lead was significantly associated with elevated blood pressure in males age 20-74 and also significantly, although with less strength, in females.

Hense HW, Filipiak B, Keil U. The association of blood lead and blood pressure in population surveys. Epidemiology 1993; 4: 173-179.

This paper reported on additional analyses of data from the MONICA Augsburg Cohort Study (1987-1988), which in crude analyses, found a strong positive association between blood lead levels and both systolic and diastolic blood pressure. After controlling for confounders, this paper reported a difference of 100 micrograms per liter (10 µg/dL) in blood lead levels related to estimated blood pressure increases of less than 3 mm Hg (millimeters of mercury).

Bushnik T, Levallois P, D'Amour M, et al. Association between blood lead and blood pressure: Results from the Canadian Health Measures Survey (2007 to 2011). Health Reports 2014; 25: 12-22.

This study, based on the Canadian Health Measures Survey (2007-2011), found a modest association (a) between blood lead levels and systolic blood pressure for 40-to-54-year-olds and (b) between blood lead levels and diastolic blood pressure for the overall population. However, the study did not find an association between blood lead levels and prevalence of hypertension.

Gambelunghe A, Sallsten G, Borné Y, et al. Low-level exposure to lead, blood pressure, and hypertension in a population-based cohort. Environmental Research 2016; 149: 157-163.

This study of low-level exposure to lead and both blood pressure and hypertension in a population-based cohort found that blood lead level was associated with significantly higher systolic and diastolic blood pressure. Specifically, the study found that blood lead level in the 4th quartile was associated with significantly higher systolic and diastolic blood pressure (point estimates: 1-2 mmHg). The study also found that blood lead levels were significantly associated with increased prevalence of hypertension (odds ratio = 1.3; 95% CI, 1.1-1.5).

Kirkby H, Gyntelberg F. Blood pressure and other cardiovascular risk factors of long-term exposure to lead. Scandinavian Journal of Work, Environment & Health 1985; 11: 15-19.

This cross-sectional study of blood pressure and other cardiovascular risk factors associated with long-term exposure to lead found that, among 96 heavily exposed lead smelter workers who had been employed between 9 and 45 years, the diastolic blood pressure was significantly lower than among a reference group of 95 workers. In the sitting position, the study found that the mean diastolic blood pressure in the lead workers was 86 compared with 82 in the referents ($P = 0.04$). In the supine position, the mean diastolic blood pressure of the lead workers was 83 compared to 78 in the referents ($P = 0.005$).

Pirkle JL, Schwartz J, Landis JR, Harlan WR. The relationship between blood lead levels and blood pressure and its cardiovascular risk implications. American Journal of Epidemiology 1985; 121: 246-258.

This paper reported on a cross-sectional analysis of white males aged 40 to 59 years in the National Health and Nutrition Examination Survey (1976-1980). After adjusting for age, nutritional factors, body mass index, and serum chemistries in a multiple regression model, blood lead levels were significantly associated with both systolic and diastolic blood pressure ($P < 0.01$).

de Kort WL, Verschoor MA, Wibowo AA, van Hemmen JJ. Occupational exposure to lead and blood pressure: A study in 105 workers. American Journal of Industrial Medicine 1987; 11: 145-156.

This cross-sectional study of 53 workers exposed to both lead and cadmium compounds found a significant correlation between blood lead level and both systolic and mean blood pressure, after controlling for age and pulse rate
($r = 0.22$; $P < 0.05$).

Hu H, Aro A, Payton M, et al. The relationship of bone and blood lead to hypertension. JAMA 1996; 275: 1171-1176.

This case-control study based on participants in the Veterans Administration Normative Aging Study (a 30-year longitudinal cohort study of 1,171 men) found, in a logistic regression model, that tibial lead concentration (as well as body mass index and family history of hypertension) were associated with hypertension. An increase from the midpoint to the lowest quintile to the midpoint of the highest quintile of tibial lead level was associated with an odds ratio of 1.5 (95% CI, 1.1-1.8). The study also found a significant association between tibial lead concentration and hypertension (odds ratio = 1.019; 95% CI, 1.004-1.035; $P = 0.01$).

Wu TN, Shen CY, Ko KN, et al. Occupational lead exposure and blood pressure. International Journal of Epidemiology 1995; 25: 791-796.

This cross-sectional study examined occupational lead exposure and blood pressure in workers at two lead battery manufacturing facilities. After considering all possible confounding variables, multivariate regression analyses showed that current blood lead level was not a significant predictor for either systolic or diastolic blood pressure.

Bost L, Primatesta P, Dong W, Poulter N. Blood lead and blood pressure: Evidence from the Health Survey for England 1995. Journal of Human Hypertension 1999; 13: 123-128.

This cross-sectional analysis estimated that halving blood lead levels would decrease diastolic blood pressure between 0.8 and 1.1 mm Hg in men. The authors concluded that their results are consistent with a small pressor effect (increase of blood pressure) of environmental lead on blood pressure.

Korrick SA, Hunter DJ, Rotnitzky A, et al. Lead and hypertension in a sample of middle-aged women. American Journal of Public Health 1999; 89: 330-335.

This paper reported on a case-control analysis of data from women in the prospective cohort Nurses' Health Study. The study found that, after adjusting for potentially confounding factors, an increase from the 10th to the 90th percentile of patella lead concentrations was associated with an almost two-fold (95% CI, 1.1-3.2) increased risk of hypertension, a statistically significant finding.

Bener A, Obineche E, Gillett M, et al. Association between blood levels of lead, blood pressure and risk of diabetes and heart disease in workers. International Archives of Occupational and Environmental Health 2001; 74: 375-378.

This cross-sectional study of 110 industrial workers exposed to lead and 110 non-industrial workers who were not exposed to lead found that industrial workers had significantly higher blood lead levels (median, 81 µg/dL) than non-industrial workers and that the lead-exposed group had significantly higher systolic and diastolic blood pressures.

Tepper A, Mueller C, Singal M, Sagar K. Blood pressure, left ventricular mass, and lead exposure in battery manufacturing workers. American Journal of Industrial Medicine 2001; 40: 63-72.

This cross-sectional study examined the relationship between blood pressure and lead exposure in battery manufacturing workers. The study found that diastolic blood pressure increased with increasing blood lead levels. There was a significant 5 mm Hg difference in mean pressure between the highest and lowest calculated cumulative measures of blood lead ($P = 0.04$).

Nomiyama K, Nomiyama H, Liu S-J, et al. Lead induced increase of blood pressure in female lead workers. Occupational and Environmental Medicine 2002; 59: 734-739.

This cross-sectional study of the association between lead and blood pressure in 193 female workers, 123 of whom had been exposed to lead, found that blood lead level of 40 µg/dL or higher was strongly associated with increased systolic or diastolic blood pressure. Among those with blood lead levels of 40 to 59 µg/dL, there was a significant increase in the prevalence of elevated systolic blood pressure (125 mm Hg or higher) (odds ratio = 4.26; 96% CI, 1.07-17.04; $P = 0.0405$). Among those with blood lead levels of 60 µg/dL or higher, the odds ratio was 7.48 (95% CI, 1.86-30.12; $P = 0.0046$). Among those with blood lead levels between 40 and 59 µg/dL, there was an association with increased diastolic blood pressure (80 mmHg or higher) (odds ratio = 2.43; 95% CI, 0.97-

6.04). Among those with blood lead levels of 60 µg/dL or higher, there was a significant association with increased diastolic blood pressure (odds ratio = 3.31; 95% CI, 1.29-8.50).

Martin D, Glass TA, Bandeen-Roche K, et al. Association of blood lead and tibia lead with blood pressure and hypertension in a community sample of older adults. American Journal of Epidemiology 2006; 163: 467-478.

This cross-sectional study examined the association between both blood lead level and tibial lead concentration with blood pressure and hypertension in a community sample of older adults. After adjusting for socioeconomic status and race/ethnicity, the study found significant associations between blood lead levels and both systolic and diastolic blood pressure.

Weaver VM, Ellis LR, Lee B-K, et al. Associations between patella lead and blood pressure in lead workers. American Journal of Industrial Medicine 2008; 51: 336-343.

This study, which analyzed cross-sectional data for 652 current and former lead workers, found that blood lead level was positively associated with systolic blood pressure.

Wells EM, Navas-Acien A, Herbstman JB, et al. Low-level lead exposure and elevations in blood pressure during pregnancy. Environmental Health Perspectives 2011; 119: 664-669.

This study found a significant association between low-level lead exposures, as reflected by umbilical-cord blood lead levels, and increases in maternal blood pressure during labor and delivery. The study found, after adjusting for confounders, that comparing blood pressure between those in the highest and those in the lowest quartile of lead exposure, there was a 6.87 mm Hg (95% CI, 1.51-12.21) increase in admission systolic blood pressure and a 4.40
mm Hg (95% CI, 0.21-8.59) increase in admission diastolic blood pressure.

Were FH, Moturi MC, Gottesfeld P, et al. Lead exposure and blood pressure among workers in diverse industrial plants in Kenya. Journal of Occupational and Environmental Hygiene 2014; 11: 706-715.

This study of lead exposure and blood pressure among industrial workers found, with multivariate regression analyses, that age, duration of work, airborne lead, and blood lead levels were significantly associated with an increase in blood pressure ($P < 0.05$).

Lu Y, Liu X, Deng Q, et al. Continuous lead exposure increases blood pressure but does not alter kidney function in adults 20-44 years of age in a lead-polluted region of China. Kidney & Blood Pressure Research 2015; 40: 207-214.

This cross-sectional study of 1,447 adults between 20 and 44 years of age in a lead-polluted region found a significant association between changes in blood lead level and changes in both systolic and diastolic blood pressure ($P = 0.001$).

Sirivarasai J, Kaojarern S, Chanprasertyothin S, et al. Environmental lead exposure, catalase gene, and markers of antioxidant and oxidative stress relation to hypertension: an analysis based on the EGAT study. Biomed Res Int 2015;2015:856319. doi: 10.1155/2015/856319.

This cross-sectional study of 332 normotensive, 432 prehypertensive, and 222 hypertensive male subjects found hypertensive subjects had significantly higher blood lead level (5.28 μg/dL) compared to normotensive (4.41 μg/dL) and prehypertensive (4.55 μg/dL) subjects ($P < 0.05$).

Meta-analyses and Systematic Reviews

Staessen JA, Bulpitt CJ, Fagard R, et al. Hypertension caused by low-level lead exposure: Myth or fact? Journal of Cardiovascular Risk 1994; 1: 87-97.

This meta-analysis of 23 studies on the association between hypertension and low-level lead exposure found a two-fold increase in blood lead levels associated with a 1.0 mm Hg increase in systolic blood pressure ($P = 0.002$) and with a 0.6 mm Hg increase in diastolic blood pressure ($P = 0.02$).

Navas-Acien A, Guallar E, Silbergeld EK, Rothenberg SJ. Lead exposure and cardiovascular disease: A systematic review. Environmental Health Perspectives 2007; 115: 472-482.

This systematic review of lead exposure and cardiovascular disease found a positive association of lead exposure with blood pressure in numerous studies that had been performed in different locations, including prospective studies. It noted that several of these studies identified a dose-response relationship. The authors concluded that "the evidence is sufficient to infer a causal relationship of lead exposure with hypertension."

Navas-Acien A, Schwartz BS, Rothenberg SJ, et al. Bone lead levels and blood pressure endpoints: A meta-analysis. Epidemiology 2008; 19: 496-504.

This meta-analysis of bone lead levels and blood pressure, based on three prospective cohort studies and five cross-sectional studies found that, for a 10 μg/g increase in tibial lead, the cross-sectional summary increases in blood pressure were 0.26 mm Hg for systolic blood pressure (95% CI, 0.02-0.50) and 0.02 mm Hg for diastolic blood pressure (95% CI, -0.15-0.19). The meta-analysis found that the summary odds ratio for hypertension was 1.04 (95% CI, 1.01-1.07), a significant association.

Bioavailability and biologic plausibility:

The predominant species of lead found in fly ash are lead chloride ($PbCl_2$) and lead sulfide (PbS).[1,2] Exposure to lead is cited by TOXNET as being causally related to increased risk of high blood pressure.[3]

The level of lead in the TVA coal ash (19 mg/kg) was slightly elevated as compared to background soils.[4] The sampling of coal ash by TVA, TDEC, and EPA showed a mean of 27, 19, 25.6 mg/kg respectively, again higher than background soils.[7] The National Toxicology Program (NTP)'s Monograph on Health Effects of Low-level Lead, 2012,[5] p. 63, concluded that:

Table 6.2 Main conclusions for cardiovascular effects in the 2006 EPA AQCD for Lead and the 2007 ATSDR Toxicological Profile for Lead
"Epidemiologic studies support the relationship between increased lead exposure and increased deleterious cardiovascular outcomes, including increased blood pressure and increased incidence of hypertension. ... (U.S. EPA 2006, pg 6-271)
"Population studies suggest that there is a significant association between bone-lead levels and elevated blood pressure" (ATSDR 2007, pg 21)

This monograph suggests that sufficient evidence for an association between lead exposure and elevated blood pressure / hypertension exists and does not require extremely high levels of lead exposure.

Biologic Mechanisms:
The pathophysiology of lead-induced hypertension has been examined in several studies. Proposed mechanisms, as reviewed by Vaziri,[6] include dysregulation of the renin-angiotensin-aldosterone system, direct effects on the endothelium and vascular smooth muscle, and stimulation of the sympathetic nervous system due to elevated production of catecholamines. Lead has been shown to promote endothelial release of endothelin; to elevate serum levels of norepinephrine, angiotensin-converting enzyme, and thromboxane; and to decrease production of prostacyclin. These changes will promote vasoconstriction.

References:

1. Nomura Y, Fujiwara K, Terada A, et al. Prevention of lead leaching from fly ashes by mechanochemical treatment. Waste Management 30 (2010) 1290–1295.

2. Tian S, Zhu Y, Meng B, et al. Chemical speciation of lead in secondary fly ash using X-ray absorption spectroscopy. Chemosphere 197 (2018) 362e366.

3. https://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+6309

4. Ruhl L, Vengosh A, Dwyer GS, et al. Survey of the Potential Environmental and Health Impacts in the Immediate Aftermath of the Coal Ash Spill in Kingston, Tennessee. Environ. Sci. Technol. 2009, 43, 6326–6333.

5. National Toxicology Program, U.S. Department of Health and Human Services.
NTP MONOGRAPH ON HEALTH EFFECTS OF LOW-LEVEL LEAD, June 13, 2012.

6. Vaziri N, Gonick H. Cardiovascular effects of lead exposure. Indian J Med Res 128, October 2008, pp 426-435.

7. Tennessee Valley Authority (TVA), Document No. EPA-AO-030, TVA Kingston Fossil Fuel Plant Release Site, On-Scene Coordinator Report for the Time-Critical Removal Action, May 11, 2009 through December 2010, Harriman, Roane County, Tennessee.

Arsenic and Coronary Artery Disease

Analysis of the following medical and scientific literature supports a causal association between exposure to arsenic in coal ash and occurrence of coronary artery disease, including acute myocardial infarction, based on satisfaction of the following Bradford Hill Principles:

Strength
Consistency
Temporality
Biologic Gradient (Dose-response Relationship)
Biologic Plausibility

A positive association between arsenic and coronary artery disease has been observed in many epidemiologic studies in different populations using several study designs, and controlling for a wide range of potentially confounding factors. In the cohort studies, exposure was measured prior to the measurement of the outcome (temporality), thus avoiding recall bias. Studies often showed positive dose-response associations. Several studies showed relative risk estimates in the moderate to strong range. Data suggesting that arsenic might enhance atherosclerosis by increasing monocyte adhesion to endothelial cells provide a plausible biologic mechanism. Based on ample published literature, several meta-analyses have been performed concluding that there is an association between arsenic and cardiovascular disease.

Cohort Studies

Lewis DR, Southwick JW, Ouellet-Hellstrom R, et al. Drinking water arsenic in Utah: A cohort mortality study. Environmental Health Perspectives 1999; 107: 359-365.

This cohort mortality study did not find an association between exposure to arsenic and ischemic heart disease.

Sohel N, Persson LA, Rahman M, et al. Arsenic in drinking water and adult mortality: A population-based cohort study in rural Bangladesh. Epidemiology 2009; 20: 824-830.

This cohort study found that, even at low levels (10 to 49 µg/L) of arsenic in drinking water, there was an increased risk of mortality from cardiovascular disease (hazard ratio = 1.16; 95% CI, 0.96-1.40). (Cardiovascular disease deaths are primarily due to coronary artery disease, including acute myocardial infarction.)

Chen Y, Graziano JH, Parvez F, et al. Arsenic exposure from drinking water and mortality from cardiovascular disease in Bangladesh: Prospective cohort study. British Medical Journal 2011; 342:d2431 doi:10.1136/bmj.d2431.

This cohort mortality study found a dose-response relationship between exposure to arsenic in well water and mortality from ischemic heart disease (coronary artery disease) and other heart disease. In increasing quartiles of arsenic concentration in well water, the hazard ratios were 1.00 (reference concentration), 1.22 (95% CI, 0.65-2.32), 1.35 (95% CI, 0.71-2.57), and 1.92 (95% CI, 1.07-3.43) (*P* for trend = 0.0019), after

adjusting for potential confounders. (Ischemic heart disease accounted for 68 of the deaths and other forms of heart disease accounted for 32.)

Gong G, O'Bryant SE. Low-level arsenic exposure, AS3MT gene polymorphism and cardiovascular diseases in rural Texas counties. Environmental Research 2012; 113: 52-57.

This cohort study found that coronary heart disease was associated with higher arsenic exposure ($P < 0.05$).

Moon KA, Guallar E, Umans JG, et al. Association between low to moderate arsenic exposure and incident cardiovascular disease: A prospective cohort study. Annals of Internal Medicine 2013; 159: 649-659.

This prospective cohort study found that urinary arsenic concentration was significantly associated with coronary heart disease (coronary artery disease) (hazard ratio = 1.71; 95% CI, 1.19-2.44; *P* for trend < 0.001).

Cross-sectional Study

Zierold KM, Knobeloch L, Anderson H. Prevalence of chronic diseases in adults exposed to arsenic-contaminated drinking water. American Journal of Public Health 2004; 94: 1936-1937.

This cross-sectional study of arsenic exposure and self-report of 9 chronic diseases, including heart attack (acute myocardial infarction) and history of coronary artery bypass graft surgery, found significant associations between arsenic concentration greater than 10 µg/L in private well water samples and both heart attack (adjusted odds ratio = 2.08; 95% CI, 1.10-4.31) and coronary artery bypass graft surgery (adjusted odds ratio = 2.34; 95% CI, 1.12-4.90).

Meta-analyses and Systematic Reviews

Navas-Acien A, Sharrett AR, Silbergeld EK, et al. Arsenic exposure and cardiovascular disease: A systematic review of the epidemiologic evidence. American Journal of Epidemiology 2005; 162: 1037-1049.

This systematic review of epidemiologic evidence concerning arsenic exposure and cardiovascular disease found that in Taiwan the relative risks for coronary (artery) disease ranged from 1.19 to 2.69, with a median relative risk of 1.94.

Moon K, Guallar E, Navas-Acien A. Arsenic exposure and cardiovascular disease: An updated systematic review. Current Atherosclerosis Reports 2012; 14: 542-555.

This meta-analysis, based on a total of 31 studies, found a significantly increased pooled relative risk for coronary heart disease (coronary artery disease) (pooled relative risk = 1.89; 95% CI, 1.33-2.69).

Ecological Studies

Chen C-J, Chiou H-Y, Chiang M-H, et al. Dose-response relationship between ischemic heart disease mortality and long-term arsenic exposure. Arteriosclerosis, Thrombosis, and Vascular Biology 1996; 16: 504-510.

This ecological study found a dose-response relationship between long-term exposure to arsenic in drinking water and mortality from ischemic heart disease (coronary artery disease). The relative risks in the three tertiles of cumulative arsenic exposure were 2.46 (95% CI, 0.53-11.37), 3.97 (95% CI, 1.01-15.59), and 6.47 (95% CI, 1.88-22.24).

Meliker JR, Wahl RL, Cameron LL, Nriagu JO. Arsenic in drinking water and cerebrovascular disease, diabetes mellitus, and kidney disease in Michigan: A standardized mortality ratio analysis. Environmental Health 2007; 6:4. doi:10.1186/1476-069X-6-4.

This ecological study found, in Genesee County, Michigan (where the median population-weighted arsenic concentration in groundwater was 8.48 µg/L, the second highest arsenic concentration among the six counties in the southeastern Michigan study area), significantly increased mortality due to ischemic heart disease (coronary artery disease). In both males and females, the SMR was 1.05 (99% CI, 1.02-1.08).

Medrano MJ, Boix R, Pastor-Barriuso R, et al. Arsenic in public water supplies and cardiovascular mortality in Spain. Environmental Research 2010; 110; 448-454.

This ecological study found that increased low-to-moderate arsenic concentrations in drinking water (greater than
10 µg/L) were associated with mortality from coronary heart disease (SMR = 1.18; 95% CI, 1.148-1.216).

Bioavailability and biologic plausibility:

The Agency for Toxic Substances and Registry (ATSDR) of the United States ranked arsenic first in its list of the twenty most hazardous substances.[1] The toxicity of arsenic is connected to its solubility and is affected by pH. Arsenite (As3+) is more soluble than arsenate (As5+) and is more toxic; however, at a lower pH, arsenate becomes more mobile and toxic. All four forms of arsenic (As^{3+}, As^{5+}, DMAA, MMAA) have adverse effects at the cell metabolism level.[2] Most of the arsenic in fly ash appears to be inorganic in the arsenate (As5+) form.[3]

On June 21, 2010 (75 FR 35128),[4] the U.S. EPA proposed to regulate coal combustion residuals (CCR) under RCRA to address the risks from the disposal of CCR generated from the combustion of coal at electric utilities and independent power producers. As described in the proposal, CCR are residuals generated from the combustion of coal and include fly ash and bottom ash. The EPA noted in the proposed rule that the constituents of most environmental concern in CCR are metals, including As. The EPA also presented data showing numerous instances where these constituents (especially arsenic) have leached at levels of concern.

An investigation of the potential environmental and health impacts in the immediate aftermath of Kingston coal ash spill found the surface release of coal ash with high levels of toxic As at 75 mg/kg; Hg 150 µg/kg, which the authors concluded could pose a health risk. They noted that the high arsenic concentration in the TVA coal ash (mean) 75 mg/kg) is consistent with previously reported As in ash residue. The ratio of As levels in the TVA coal ash to As levels in background soil was 21.4, indicating very high elevated levels of As in the TVA coal ash.[5] Similar levels were found by agency sampling with TVA, TDEC, and EPA finding a mean of 65, 73, and 61.1 mg/kg respectively.[8]

Biologic Mechanisms:

Stea et al., 2016[6] examined arsenic (As) exposure and arterial intima-media thickness (IMT) among 214 healthy volunteers, age 20 to 46, stratified by polymorphisms in GSTT1. Subjects with higher urinary As level (≥3.86 µg/L) and carriers of the GSTT1-positive (+) genotype also had higher IMT than those with a low urinary level and the GSTT1-null (−) genotype (0.56 [0.48–0.64] vs. 0.53 [0.44–0.62] mm, p = 0.010). The analysis hints at faster vascular aging in persons exposed to higher levels of As compared with the healthy population.

Lemaire et al., 2015[7] observed that As induces human monocyte adhesion to endothelial cells in vitro. These findings were confirmed ex vivo using a murine organ culture system at concentrations as low as 10 ppb. This adhesion process is specific to monocyte/endothelium interactions. Hence, no effect of arsenic on platelet activation or platelet/leukocyte interaction was observed. They found that arsenic increases adhesion of mononuclear cells via increased CD29 binding to VCAM-1, an adhesion molecule found on activated endothelial cells. Similar results were observed in vivo, where arsenic-exposed mice exhibit increased VCAM-1 expression on endothelial cells and increased CD29 on circulating monocytes. Together, these data suggest that arsenic might enhance atherosclerosis by increasing monocyte adhesion to endothelial cells.

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8. Tennessee Valley Authority (TVA), Document No. EPA-AO-030, TVA Kingston Fossil Fuel Plant Release Site, On-Scene Coordinator Report for the Time-Critical Removal Action, May 11, 2009 through December 2010, Harriman, Roane County, Tennessee.

Cadmium and Coronary Artery Disease

Analysis of the following medical and scientific literature supports a causal association between exposure to cadmium in coal ash and occurrence of coronary artery disease, based on satisfaction of the following Bradford Hill Principles:

Strength
Consistency
Temporality
Plausibility

A positive association between cadmium and coronary artery disease has been observed in several epidemiologic studies in different populations using several study designs, and controlling for a wide range of potentially confounding factors. In the cohort studies, exposure was measured prior to the measurement of the outcome (temporality), thus avoiding recall bias. Studies often showed positive dose-response associations. Several studies showed relative risk estimates in the moderate to strong range. Multiple plausible mechanisms have been suggested, including those related to oxidative stress, inflammation, endothelial dysfunction, enhanced lipid synthesis, upregulation of adhesion molecules, prostanoid dysbalance, and altered glycosaminoglycan synthesis. Based on sufficient published literature, a meta-analysis was performed concluding that there is an association between cadmium and cardiovascular disease.

Cohort Studies

Fagerberg B, Bergstrom G, Boren J, et al. Cadmium exposure, intercellular adhesion molecule-1 and peripheral artery disease: a cohort and an experimental study. BMJ Open 2013;3:e002489. doi:10.1136/bmjopen-2012-002489

> This prospective cohort study found that blood cadmium concentrations above 0.44 µg/l and urinary cadmium levels above 0.46 µg/g creatine were associated with an increased risk that was greater than two-fold for peripheral artery disease in comparison with participants in the lowest tertiles of cadmium exposure after 5.4 years of follow-up. This increase in risk remained for blood cadmium levels after exclusion of participants with plaques in the right femoral artery and adjustment for pack-years, current smoking and other cardiovascular risk factors at baseline.

Barregard L, Sallsten G, Fagerberg B, et al. Blood Cadmium Levels and Incident Cardiovascular Events during Follow-up in a Population-Based Cohort of Swedish Adults: The Malmö Diet and Cancer Study. Environ Health Perspect. 2016 May;124(5):594-600. doi: 10.1289/ehp.1509735. Epub 2015 Oct 30.

> In this cohort study, hazard ratios for all cardiovascular end points were consistently increased for participants in the 4th blood cadmium quartile (median, 0.99 µg/L). In models that also included sex, smoking, waist circumference, education, physical

activity, alcohol intake, serum triglycerides, HbA1c, and C-reactive protein, the hazard ratios comparing the highest and lowest quartiles of exposure were 1.8 (95% CI: 1.2, 2.7) for acute coronary events.

Case-Control Studies

Cebi A, Kaya Y, Gungor H, et al. Trace elements, heavy metals and vitamin levels in patients with coronary artery disease. International Journal of Medicine Sciences 2011; 8: 456-460.

This case-control study did not find a significant difference in the serum levels of cadmium between patients with coronary artery disease and control subjects.

Cross-sectional Study

Sponder M, Fritzer-Szekeres M, Marculescu R, et al. Blood and urine levels of heavy metal pollutants in female and male patients with coronary artery disease. Vascular Health and Risk Management 2014; 10: 311-317.

This cross-sectional study found that urinary levels of cadmium detected in patients with coronary artery disease were high compared to reference levels (0.67 µg/L vs. 0.335 µg/L).

Mendy A, Gasana J, Vierira ER. Urinary heavy metals and associated medical conditions in the US adult population. International Journal of Environmental Health Research 2012; 22: 105-118.

This publication, based on data from the 2007-2008 National Health and Nutrition Examination Survey, found a significant association between cadmium and cardiovascular diseases (odds ratio = 4.94; 95% CI, 1.48-16.56).

Agarwal S, Zaman T, Tuzcu EM, Kapadia SR. Heavy metals and cardiovascular disease: Results from the National Health and Nutrition Examination Survey (NHANES) 1999-2006. Angiology 2011; 62: 422-429.

This cross-sectional study found a significant association between urinary cadmium and cardiovascular and cerebrovascular disease combined (adjusted odds ratio = 2.35; 95% CI, 1.47-3.75).

Asgary S, Movahedian A, Keshvari M, et al. Serum levels of lead, mercury and cadmium in relation to coronary artery disease in the elderly: A cross-sectional study. Chemosphere 2017; 180: 540-544.

This cross-sectional study found that the serum concentration of cadmium was significantly higher in patients who had angiographically-documented coronary artery disease than in healthy control subjects (0.938; 95% CI, 0.866-1.010 vs. 0.448 (95% CI, 0.418-0.478; $P < 0.05$).

Meta-Analysis

Tinkoy AA, Filippini T, Aisuvakova OP, et al. Cadmium and atherosclerosis: A review of toxicological mechanisms and a meta-analysis of epidemiologic studies. Environmental Research 162 (2018) 240–260.

> A systematic search of the PubMed-Medline database through December 20, 2017. Elevated urinary Cd levels were associated with increased mortality for cardiovascular disease (HR = 1.34, 95% CI: 1.07–1.67) as well as elevated blood Cd levels (HR = 1.78, 95% CI: 1.24–2.56). The results of meta-analysis demonstrate that Cd exposure is associated with higher prevalence and mortality from CVD, including CHD, stroke and PAD.

Bioavailability and biologic plausibility:

The EPA has determined Cd in coal ash has the potential to be a potentially harmful contaminant.[1] The ratio of Cd levels in the TVA coal ash to Cd levels in background soil was 3.0, indicating considerably elevated levels of Cd in the TVA coal ash.[2] Significantly higher levels were found by the EPA with a mean of 0.86 mg/kg.[4]

Mechanisms:
The systematic review of toxicological mechanisms for cadmium (Cd) exposure and coronary artery disease[3] noted consistently observed associations between Cd exposure markers (blood and urine) and coronary heart disease, stroke, and peripheral artery disease. Cd exposure was also associated with atherogenic changes in lipid profile. The authors of the meta-analysis noted that both experimental and clinical studies suggest an adverse effect of Cd on atherogenesis, which may occur through multiple mechanisms, including oxidative stress, inflammation, endothelial dysfunction, enhanced lipid synthesis, upregulation of adhesion molecules, prostanoid dysbalance, as well as altered glycosaminoglycan synthesis.

References

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3. Tinkoy et al. (meta-analysis shown above)

4. Tennessee Valley Authority (TVA), Document No. EPA-AO-030, TVA Kingston Fossil Fuel Plant Release Site, On-Scene Coordinator Report for the Time-Critical Removal Action, May 11, 2009 through December 2010, Harriman, Roane County, Tennessee.

Fine Particulate Matter and Coronary Artery Disease,
Including Acute Myocardial Infarction

Fine particulate matter is particles having an aerodynamic diameter of 2.5 μ (microns) or less. Analysis of the following medical and scientific literature supports a causal association between exposure to fine particulate matter in coal ash and occurrence of coronary artery disease, including acute myocardial infarction, based on satisfaction of the following Bradford Hill:

Strength
Consistency
Temporality
Biologic Gradient (Dose-response Relationship)
Biologic Plausibility

A positive association between fine particulate matter and coronary artery disease has been observed in many epidemiologic studies in different populations using several study designs, and controlling for a wide range of potentially confounding factors. In the cohort studies, exposure was measured prior to the measurement of the outcome (temporality), thus avoiding recall bias. Studies often showed positive dose-response associations. Several studies showed relative risk estimates in the moderate to strong range. Plausible biologic mechanisms include increased generation of reactive oxygen species followed by activation of proinflammatory and prothrombotic pathways.

Cohort Studies

Laden F, Schwartz J, Speizer FE, Dockery DW. Reduction in fine particulate air pollution and mortality: Extended follow-up of the Harvard Six Cities Study. American Journal of Respiratory and Critical Care Medicine 2006; 173: 667-672.

This report from the Harvard Six Cities Study found that each 10 $\mu g/m^3$ increase in fine particulate matter was associated with a significant increase in cardiovascular mortality (relative risk = 1.28; 95% CI, 1.13-1.44). (The majority of deaths due to cardiovascular disease are due to coronary artery disease, including acute myocardial infarction.) The study also found that cardiovascular mortality was positively associated with average airborne concentration of fine particulate matter during the entire follow-up period ($P < 0.0001$).

Hoffmann B, Moebus S, Möhlenkamp S, et al. Residential exposure to traffic is associated with coronary atherosclerosis. Circulation 2007; 116: 489-496.

This cohort study was designed to investigate associations of long-term residential exposure to traffic and fine particulate matter with the degree of coronary athero-sclerosis. The main outcome measure was coronary artery calcification (CAC). In comparison to study participants living more than 200 meters from a major roadway: (a) participants living within 50 meters of a major roadway were significantly more likely to have a high CAC (odds ratio = 1.63; 95% CI, 1.14-2.23); (b) participants living between 51

and 100 meters of a major roadway were more likely to have a high CAC, an association of borderline significance (odds ratio = 1.34; 95% CI, 1.00-1.79); and (c) participants living between 101 and 200 meters of a major roadway were more likely to have a high CAC, an association that was not statistically significant (odds ratio = 1.08; 95% CI, 0.85-1.39). Exposure to fine particulate matter was associated with CAC only in subjects who had not been working full-time for at least 5 years.

Lepeule J, Laden F, Dockery D, Schwartz J. Chronic exposure to fine particles and mortality: An extended follow-up of the Harvard Six Cities Study from 1974 to 2009. Environmental Health Perspectives 2012; 120: 965-970.

This report from the Harvard Six Cities Study found that average airborne fine particulate matter levels were significantly associated with cardiovascular mortality, a significant increase of 26% (95% CI, 14%-40%). The study demonstrated a linear concentration-response relationship between fine particulate matter and cardiovascular mortality.

Dorans JS, Wilker EH, Li W, et al. Residential proximity to major roads, exposure to fine particulate matter, and coronary artery calcium. Arterosclerosis, Thrombosis, and Vascular Biology 2016; 36: 1679-1685.

This cohort study, performed in a region with relatively low levels of and little variation in fine particulate matter, did not find any consistent associations between either residential distance to a major roadway or a residential fine particulate matter with detectable CAC.

Hartiala J, Breton CV, Wang HW, et al. Ambient air pollution is associated with the severity of coronary atherosclerosis and incident myocardial infarction in patients undergoing elective cardiac evaluation. Journal of the American Heart Association 2016; 5:e003947 doi: 10.116/JAHA.116.003947.

This prospective cohort study found a significant association between severe coronary artery disease and exposure to fine particulate matter (odds ratio = 1.63; 95% CI, 1.26-2.11; $P < 0.0001$). The study also found that exposure to higher fine particulate matter levels was significantly associated with increased risk of incident acute myocardial infarction (hazard ratio = 1.33; 95% CI, 1.02-1.73; $P = 0.03$).

Thurston GD, Burnett RT, Turner MC, et al. Ischemic heart disease mortality and long-term exposure to source-related components of U.S. fine particle air pollution. Environmental Health Perspective 2016; 124: 785-794.

This cohort mortality study found that associations between ischemic heart disease (coronary artery disease) mortality varied by both mass constituent and source of fine particulate matter. The study found, for example, that fine particulate matter from coal combustion was significantly associated with ischemic heart disease mortality (hazard ratio = 1.05; 95% CI, 1.02-1.08, per microgram per cubic meter).

McGuinn LA, Ward-Caviness C, Neas LM, et al. Fine particulate matter and cardiovascular disease: Comparison of assessment methods for long-term exposure. Environmental Research 2017; 159: 16-23.

This cohort study found an association between fine particulate matter and both a high coronary disease risk score and a recent myocardial infarction. For example, the study found a significant association between a 1 $\mu g/m^3$ increase in annual average fine particulate matter and coronary artery disease (odds ratio = 1.13; 95% CI, 1.06-1.21) based on satellite-based estimates of fine particulate matter.

Case-crossover Studies

Pope CA III, Muhlestein MB, Anderson JL, et al. Short-term exposure to fine particulate matter air pollution is preferentially associated with the risk of ST-segment elevation acute coronary events. Journal of the American Heart Association 2015; 4:e002506 doi: 10.1161/JAHA.115.002506.

This case-crossover study, in which patients served as their own controls, found significant associations between short-term exposure to fine particulate matter and acute coronary events with ST-segment elevation. For example, the study found in patients with angiographic evidence of coronary artery disease, the odds ratio for a 10 $\mu g/m^3$ increase in concurrent-day fine particulate matter air pollution greater than 25 $\mu g/m^3$ was 1.15 (95% CI, 1.03-1.29) for acute myocardial infarction with ST-segment elevation.

Rich DQ, Kipen HM, Zhang J, et al. Triggering of Transmural Infarctions, but Not Nontransmural Infarctions, by Ambient Fine Particles. Environ Health Perspect 118:1229–1234 (2010).

This study showed that each interquartile-range increase in PM2.5 concentration (10.8 $\mu g/m^3$) in the 24 hours before arriving at the emergency department for MI was associated with an increased risk of a transmural infarction, but not non-transmural infarction, particularly in subjects with preexisting COPD.

Ecological Study

Chen R, Yin P, Meng X, et al. Fine particulate air pollution and daily mortality: A nationwide analysis in 272 Chinese cities. American Journal of Respiratory and Critical Care Medicine 2017; 196: 73-81.

This ecological study found that each 10 $\mu g/m^3$ increase in 2-day moving average of fine particulate matter concentrations was significantly associated with an increment in mortality of 0.30% from coronary heart diseases.

Biologic Mechanisms:

Inflammation has long been linked with exposure to particulates. For example, Dabass et al.[1] observed a significant effect of PM2.5 acutely at lag day 0 on CRP level; a 10 μg/m3 rise in lag day 0 PM2.5 level was associated with a 10.1% increase (95% CI: 2.2–18.6%) in CRP levels for participants with metabolic syndrome. In their review of mechanisms, Simkhovich and colleagues[2] concluded: "Short-term and long-term studies clearly indicate that relatively modest exposures to particulate matter in the ambient air are associated with increased morbidity and mortality due to coronary heart disease. In humans, inhalational exposure to particulate air pollutants decreases heart rate variability, causes ST-segment depression and endothelial dysfunction, increases blood pressure and blood coagulability, and accelerates the progression of atherosclerosis. Mechanisms of air pollution-induced cardiotoxicity include increased generation of reactive oxygen species followed by activation of proinflammatory and prothrombotic pathways. In experimental settings, ultrafine air pollutants instilled directly into the cardiac vasculature depress cardiac contractility and decrease coronary flow." Whereas many of the studies reviewed examined long-term exposure to particulates,[3] a meta-analysis of ecological time series studies of short-term exposure to outdoor PM2.5 found evidence for adverse effects of short-term exposure to PM2.5 on CVD mortality and hospitalizations.[4] Fine particulate matter is abundant in coal ash.[5]

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4. Atkinson R, Kang S, Anderson H, et al. Epidemiological time series studies of PM2.5 and daily mortality and hospital admissions: a systematic review and meta-analysis. Thorax 2014;69:660-665. doi:10.1136/thoraxjnl-2013-204492.

5. Thriveni. T, Ramakrishna. CH , Seong Young Nam, et al. Monitoring of PM2.5 in coal ash samples & heavy metals stabilization by carbonation method. 2017 World of Coal Ash (WOCA) Conference in Lexington, KY - May 9-11, 2017 http://www.flyash.info/

Arsenic and Lung Cancer

Analysis of the following medical and scientific literature supports a causal association between exposure to arsenic in coal ash and occurrence of lung cancer, based on satisfaction of the following Bradford Hill Principles:

Strength
Consistency
Temporality
Biologic Gradient (Dose-response Relationship)
Plausibility

A positive association between arsenic and lung cancer has been observed in several epidemiologic studies in different populations using several study designs, and controlling for a wide range of potentially confounding factors. In the cohort studies, exposure was measured prior to the measurement of the outcome (temporality), thus avoiding recall bias. Studies often showed positive dose-response associations. Several studies showed relative risk estimated in the moderate to strong range. Arsenic damaging cell DNA and reacting with critical sulfhydryl-containing enzymes provide plausible underlying biologic mechanisms. Based on ample published literature, several meta-analyses were performed concluding that there is an association between arsenic and lung cancer.

Cohort Studies

Tsuda T, Babazono A, Yamamoto E, et al. Ingested arsenic and internal cancer: A historical cohort study followed for 33 years. American Journal of Epidemiology 1995; 141: 198-209.

This cohort study was of 454 residents in an arsenic-polluted area in Japan who used well water containing inorganic arsenic. Among those residents who had been exposed to arsenic concentrations of 1 ppm or greater in their drinking water, there was significantly elevated mortality due to lung cancer (standardized mortality ratio [SMR] = 15.69; 95% confidence interval [CI], 7.38-31.02).

Chen C-L, Hsu L-I, Chiou H-Y, et al. Ingested arsenic, cigarette smoking, and lung cancer risk: A follow-up study in arseniasis-endemic areas in Taiwan. JAMA 2004; 292: 2984-2990.

This cohort study of 2,503 residents in an area in Taiwan, where the drinking water was contaminated with arsenic, found significantly increased lung cancer among those who had been exposed to arsenic levels in well water of
100 µg/L or higher. For example, among those who had been exposed to 100-299 µg/L of arsenic in their drinking water, the relative risk was 2.28 (95% CI, 1.22-4.27). There was a significant dose-response relationship between ingested arsenic and lung cancer risk, more prominent among cigarette smokers.

Chen J-G, Chen Y-G, Zhou Y-S, et al. A follow-up study of mortality among the arseniasis patients exposed to indoor combustion of high arsenic coal in Southwest Guizhou Autonomous

Prefecture, China. International Archives of Occupational and Environmental Medicine 2007; 81: 9-17.

This cohort study of arseniasis patients exposed to indoor combustion of high-arsenic coal in China found significantly increased mortality due to lung cancer (SMR = 2.84; 95% CI, 1.51-4.86).

Baastrup R, Sørensen M, Balstrøm T, et al. Arsenic in drinking-water and risk for cancer in Denmark. Environmental Health Perspectives 2008; 116: 231-237.

This prospective cohort study of 57,053 persons in the Copenhagen and Aarhus areas of Denmark did not find an increased incidence rate ratio for lung cancer in association with arsenic exposure.

Taeger D, Krahn U, Wiethege T, et al. A study on lung cancer mortality related to radon, quartz, and arsenic exposures in German uranium miners. Journal of Toxicology and Environmental Health, Part A 2008; 71: 859-865.

This cohort mortality study of German uranium miners who had been exposed to radon, quartz (containing crystalline silica), and arsenic, found significantly increased proportional lung cancer mortality (age- and calendar-year adjusted standardized proportional mortality ratio = 2.86; 95% CI, 2.72-3.01). Among all miners, the risk of lung cancer was significantly increased among those who had exposure up to 125.83 $\mu g/m^3$ x years (odds ratio = 1.43; 95% CI, 1.27-1.60).

Garcia-Esquinas E, Pollán J, Umans JG, et al. Arsenic exposure and cancer mortality in a US-based prospective cohort: The Strong Heart Study. Cancer Epidemiology, Biomarkers and Prevention 2013; 22: doi:10.1158/1055-9965.EPI-13-0234-T.

This cohort study of arsenic exposure and cancer mortality in 3,932 American Indians age 45 to 74 from Arizona, Oklahoma, North Dakota, and South Dakota found significantly increased mortality due to lung cancer (adjusted hazard ratio = 1.56; 95% CI, 1.02-2.39).

Steinmaus C, Ferreccio C, Romo JA, et al. Drinking water arsenic in northern Chile: High cancer risks 40 years after exposure cessation. Cancer Epidemiology, Biomarkers and Prevention 2013; 22. doi.10.1158/1055-9965.EPI-12-1190.

This study of cancer incidence in adults after in-utero and early-life exposure to arsenic in drinking water found significantly increased incidence of lung cancer (in the highest exposure category, odds ratio = 5.24; 95% CI, 3.05-9.00). There was also a statistically significant dose-response relationship.

Case-Control Studies

Chen C-J, Chuang Y-C, You S-L, et al. A retrospective study on malignant neoplasms of bladder, lung and liver in blackfoot disease endemic area in Taiwan. British Journal of Cancer 1986; 53; 399-405.

This case-control study performed in an area with high arsenic concentrations in well water found, among those who had used well water for 40 or more years, significantly increased lung cancer (adjusted odds ratio = 3.39).

Chen C-J, Wu M-M, Lee S-S, et al. Atherogenicity and carcinogenicity of high-arsenic artesian well water: Multiple risk factors and related malignant neoplasms of blackfoot disease. Arteriosclerosis 1988; 8: 452-460.

This case-control study in an area with high arsenic concentrations in artesian well water found significantly increased mortality due to lung cancer (SMR based on residents in the blackfoot disease-endemic area = 284).

Chiou H-Y, Hsueh Y-M, Liaw K-F, et al. Incidence of internal cancers and ingested inorganic arsenic: A seven-year follow-up study in Taiwan. Cancer Research 1995; 55: 1296-1300.

This case-control study in an area where there were high concentrations of arsenic in artesian well water found significantly increased lung cancer incidence among those who had been exposed to 20 or more mg/L x year arsenic in drinking water (relative risk = 4.01; 95% CI, 1.00-16.12,
$P < 0.05$).

Ferreccio C, González C, Milosavjlevic V, et al. Lung cancer and arsenic concentrations in drinking water in Chile. Epidemiology 2000; 11: 673-679.

This case-control study found a dose-response relationship between arsenic concentration and lung cancer. Among those exposed to an average water concentration of arsenic of 50 to 199 µg/L, the odds ratio estimate was 3.9 (95% CI, 1.7-9.1) and among those who had been exposed to 200 to
400 µg/L, the odds ratio estimate was 7.7 (95% CI, 3.3-17.8).

Heck JE, Andrew AS, Onega T, et al. Lung cancer in a U.S. population with low to moderate arsenic exposure. Environmental Health Perspectives 2009; 117: 1718-1723.

This study found a significant association between small cell lung cancer and squamous cell carcinoma of the lung combined and low to moderate arsenic exposure, based on levels of toenail arsenic. For example, among those who had toenail arsenic concentration between 0.05 and less than 0.0768 µg/g, the odds ratio was 2.99 (95% CI, 1.12-7.99).

Steinmaus C, Yuan Y, Kalman D, et al. Individual differences in arsenic metabolism and lung cancer in a case-control study in Cordoba, Argentina. Toxicology and Applied Pharmacology 2010; 247: 138-145.

This case-control study focused on individual differences in arsenic metabolism and lung cancer. Among those who had high percentages of monomethylarsenic (MMA), there was a significantly increased risk of lung cancer (odds ratio = 3.09; 95% CI, 1.08-8.81).

Dauphine DC, Smith AH, Yuan Y, et al. Case-control study of arsenic in drinking water and lung cancer in California and Nevada. International Journal of Environmental Research and Public Health 2013; 10: 3310-3324.

This case-control study of arsenic in drinking water and lung cancer found an association between highest 5-year average arsenic concentration in drinking water and lung cancer in western Nevada and central California. Among those whose highest 5-year average exposure was 85 or more µg/L, the odds ratio was 1.39 (95% CI, 0.55-3.53).

Ferreccio C, Yuan Y, Calle J, et al. Arsenic, tobacco smoke, and occupation: Associations of multiple agents with lung and bladder cancer. Epidemiology 2013; 24: 898-905.

This case-control study investigated the relationship between arsenic and tobacco smoke with lung cancer and bladder cancer. Among those who smoked more than 10 cigarettes a day and had been exposed to arsenic concentrations greater than 335 µg/L in water, the odds ratio was 16 (95% CI, 6.5-40) compared to never-smokers exposed to this concentration of arsenic in water (odds ratio = 2.0; 95% CI, 0.8-5.0). Among those who had been exposed to less than 11 µg/L in water and had smoked more than 10 cigarettes a day, the odds ratio was 3.8 (95% CI, 1.7-8.5).

Steinmaus C, Ferreccio C, Romo JA, et al. Drinking water arsenic in northern Chile: High cancer risks 40 years after exposure cessation. Cancer Epidemiology, Biomarkers and Prevention 2013; 22. doi.10.1158/1055-9965.EPI-12-1190.

This case-control study in a city in northern Chile where more than 250,000 people had been exposed to high arsenic concentrations in drinking water from 1958 until 1970, when a water treatment plant was installed, found that those who had been highly exposed to arsenic in drinking water during the 1958-1970 period had significantly increased lung cancer (odds ratio = 4.35; 95% CI, 2.57-7.36).

Melak D, Ferreccio C, Kalman D, et al. Arsenic methylation and lung and bladder cancer in a case-control study in northern Chile. Toxicology and Applied Pharmacology 2014; 274: doi:10.1016/j.taap.2013.11.014.

This case-control study found a significant dose-response relationship between the proportion of urinary arsenic as monomethylarsonic acid (%MMA) and lung cancer.

Steinmaus C, Ferreccio C, Yuan Y, et al. Elevated lung cancer in younger adults and low concentrations of arsenic in water. American Journal of Epidemiology 2014; 180: 1082-1087.

This case-control study in northern Chile found an association between lung cancer and relatively low exposure to arsenic in water. Among those who had been exposed to less than 100 µg/L of arsenic in drinking water, there was a significant dose-response relationship, with a significant association in the highest tertile of arsenic exposure and lung cancer (adjusted odds ratio = 2.01; 90% CI, 1.14-3.52).

Meta-analyses and Systematic Reviews

Hertz-Picciotto I, Smith AH, Holtzman D, et al. Synergism between occupational arsenic exposure and smoking in the induction of lung cancer. Epidemiology 1992; 3: 23-31.

This study found evidence for a synergistic relationship between occupational arsenic exposure and cigarette smoking in the induction of lung cancer.

Hertz-Picciotto I, Smith AH. Observations on the dose-response curve for arsenic exposure and lung cancer. Scandinavian Journal of Work, Environment & Health 1993; 19: 217-226.

This study, which pooled data from six occupational studies in three countries, found that all of the studies with quantitative data consistently demonstrate a supralinear dose-response relationship between arsenic exposure and lung cancer.

Lamm SH, Ferdosi H, Dissen EK, et al. A systematic review and meta-regression analysis of lung cancer risk and inorganic arsenic in drinking water. International Journal of Environmental Research and Public Health 2015; 12: 15498-15515.

This meta-analysis found mortality due to lung cancer with exposures to arsenic in drinking water of 200 µg/L and higher. For example, in the range between 200 and 300 µg/L, the SMR was 4.10 (95% CI, 3.01-5.44).

Gamboa-Loira B, Cebrián ME, Franco-Marina F, López-Carrillo L. Arsenic metabolism and cancer risk: A meta-analysis. Environmental Research 2017; 156: 551-558.

This meta-analysis found that the risk of lung cancer was increased in individuals in whom there was a high percentage of monomethylated arsenic (%MMA). The summary risk estimate for lung cancer was odds ratio = 2.44 (95% CI, 1.57-3.80).

Bioavailability and biologic mechanisms:

The American Cancer Society evaluated information from several national and international health organizations to evaluate the cancer risks associated with arsenic exposure based on evidence from laboratory, animal, and human research studies.[1] These agencies include The U.S. National Toxicology Program, the International Agency for Research on Cancer (IARC), and the U.S. EPA. These agencies, as well as the American Cancer Society's own review, conclude that inorganic arsenic exposure (inhalation and ingestion) is causally linked with cancers of the lung. In an ecological study, arsenic alone was associated with 5,297 excess cases of lung cancer in the United States per year, where higher rates of lung cancer were seen in areas of higher arsenic concentrations even after controlling for smoking and income.[2] Whereas the organic arsenic compounds, such as MSMA, are considered less toxic than the inorganic forms that predominate in the TVA coal ash,[3] these methylated organic acids are also considered carcinogenic and management practices for their use are heavily emphasized today.

Arsenic and its metabolites are believed to have adverse influences at the cell level by damaging cell DNA or by reacting with critical sulfhydryl-containing enzymes. By damaging DNA, arsenic directly causes changes to occur in the formation of proteins and enzymes. While arsenic is not believed to cause point mutations in cells, it was known to cause sister chromatid exchanges (SCEs), chromatid aberrations, aneuploidy, polyploidy, DNA amplification and morphological transformations.[4,5]

There may be potential variation of arsenic carcinogenesis by route of exposure (e.g., arsenic inhalation causes primarily lung cancer, whereas arsenic ingestion causes primarily squamous cell carcinoma cancer) and exposure level.[6,7]

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3. Ruhl L, Vengosh A, Dwyer GS, et al. Survey of the Potential Environmental and Health Impacts in the Immediate Aftermath of the Coal Ash Spill in Kingston, Tennessee. Environ. Sci. Technol. 2009, 43, 6326–6333.

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Chromium and Lung Cancer

Analysis of the following medical and scientific literature supports a causal association between exposure to chromium in coal ash and occurrence of lung cancer, based on satisfaction of the following Bradford Hill Principles:

Strength
Consistency
Temporality
Biologic Gradient (Dose-response Relationship)
Plausibility
Coherence

A positive association between chromium and lung cancer has been observed in many epidemiologic studies over several decades among studies of different populations using several study designs, and controlling for a wide range of potentially confounding factors. In the cohort studies, exposure was measured prior to the measurement of the outcome (temporality), thus avoiding recall bias. Studies often showed positive dose-response associations. Several studies showed relative risk estimated in the moderate to strong range. Several biologically plausible mechanisms have been proposed, including those related to base modification, single-strand breaks, double-strand breaks, Cr-DNA adducts, DNA-Cr-DNA adducts, base pair stacking, and protein-Cr-DNA adducts, cell growth arrest, cytotoxicity, and apoptosis, and mutations. Based on ample published literature, several meta-analyses have been performed concluding that there is an association between chromium and lung cancer.

Cohort Studies

Sheffet A, Thind I, Miller AM, Louria DB. Cancer mortality in a pigment plant utilizing lead and zinc chromates. Archives of Environmental Health 1982; 37: 44-52.

This cohort mortality study of workers in a pigment plant using lead and zinc chromates found a significant increase in lung cancer among white males (relative risk = 1.6).

Franchini I, Magnani F, Mutti A. Mortality experience among chromeplating workers: Initial findings. Scandinavian Journal of Work, Environment & Health 1983; 9: 247-252.

This cohort mortality study of chromeplating workers found significantly increased lung cancer mortality among chromium platers (3 deaths observed vs. 0.7 expected; $P = 0.03$).

Langård S, Vigander T. Occurrence of lung cancer in workers producing chromium pigments. British Journal of Industrial Medicine 1983; 40: 71-74.

This cohort mortality study of workers producing chromium pigments who had been employed for 3 or more years found an increase observed/expected ratio for lung cancer (44).

Sorahan T, Burges DCL, Waterhouse JAH. A mortality study of nickel/chromium platers. British Journal of Industrial Medicine 1987; 44: 250-258.

This cohort mortality study of nickel/chromium platers found 72 deaths versus 18.1 expected, a significant increase.

Hayes RB, Sheffet A, Spirtas R. Cancer mortality among a cohort of chromium pigment workers. American Journal of Industrial Medicine 1989; 16: 127-133.

This cohort mortality study of chromium pigment workers found a significant trend between total number of years of exposure to chromate dusts and respiratory cancer mortality, as well as a significant trend between total number of years of employment in the factory and respiratory cancer mortality.

Langård S, Andersen A, Ravnestad J. Incidence of cancer among ferrochromium and ferrosilicon workers: An extended observation period. British Journal of Industrial Medicine 1990; 47: 14-19.

This cohort study of cancer incidence among ferrochromium and ferrosilicon workers found increased incidence of lung cancer (SIR = 154 among those employed before 1965).

Horiguchi S, Morinaga K, Endo G. Epidemiological study of mortality from cancer among chromium platers. Asia-Pacific Journal of Public Health 1990; 4: 169-174.

This cohort mortality study of chromium platers found increased mortality due to lung cancer (SMR = 1.13).

Moulin JJ, Portefaix P, Wild P, et l. Mortality study among workers producing ferroalloys and stainless steel in France. British Journal of Industrial Medicine 1990; 47: 537-543.

This cohort mortality study among workers producing ferroalloys and stainless steel found a significant excess of lung cancer mortality among exposed workers (11 deaths observed, SMR = 2.04), compared with non-exposed workers (SMR = 0.32).

Takahashi K, Okubo T. A prospective cohort study of chromium plating workers in Japan. Archives of Environmental Health 1990; 45: 107-111.

This prospective cohort study of chromium plating workers found significantly increased mortality for lung cancer (16 deaths observed vs. 8.9 expected; SMR = 179; 95% CI, 102-290).

Steenland K, Beaumont J, Elliot L. Lung cancer in mild steel welders. American Journal of Epidemiology 1991; 133: 220-229.

This cohort mortality study of mild steel workers found increased mortality due to lung cancer among welders
(SMR = 1.07) and non-welders (SMR = 1.17).

Moulin JJ, Wild P, Haguenoer JM, et al. A mortality study among mild steel and stainless steel welders. British Journal of Industrial Medicine 1993; 50: 234-243.

This cohort mortality study of mild stainless steel welders found increased mortality due to lung cancer (SMR = 1.24; 95% CI, 0.75-1.94). This study also found that mortality for lung cancer for mild steel welders tended to increase with duration of exposure and time since first exposure leading to significant excesses for duration of 20 or more years (SMR = 3.24; 95% CI, 1.05-7.55) and latency of 20 or more years (SMR = 2.42; 95% CI, 1.05-4.78).

Moulin JJ, Wild P, Mantout B, et al. Mortality from lung cancer and cardiovascular diseases among stainless-steel producing workers. Cancer Causes and Control 1993; 4: 75-81.

This cohort mortality study of stainless-steel producing workers found significantly increased mortality among stainless steel foundry workers (SMR = 2.29; 95% CI, 1.14-4.09).

Alexander BH, Checkoway H, Wechsler L, et al. Lung cancer in chromate-exposed aerospace workers. Journal of Occupational and Environmental Medicine 1996; 38: 1253-1258.

This cohort incidence study of chromium-exposed aerospace workers did not find a clear association between chromate exposure and risk of lung cancer in this population of workers.

Rosenman KD, Stanbury M. Risk of lung cancer among former chromium smelter workers. American Journal of Industrial Medicine 1996; 29: 491-500.

This cohort mortality study found increased lung cancer mortality among former chromium smelter workers: among white men, the proportionate cancer mortality ratio was 1.51 (95% CI, 1.29-1.74); among black men, the proportionate cancer mortality ratio was 1.34 (95% CI, 1.00-1.75). The PMCR for greater than 20 years duration of work and more than 20 years since first exposure was, for white men, 1.94 (95% CI, 1.15-3.06), and, for black men, 3.06 (95% CI, 1.13-6.71).

Mancuso TF. Chromium as an industrial carcinogen: Part I. American Journal of Industrial Medicine 1997; 31: 129-139.

This publication reported on lung cancer mortality in successive cohorts of workers at a plant manufacturing chromates. The study found a dose-response relationship between lung cancer mortality rates and exposure to chromium.

Sorahan T, Burges DCL, Hamilton L, Harrington JM. Lung cancer mortality in nickel/chromium platers, 1946-95. Occupational and Environmental Medicine 1998; 55: 236-242.

This cohort mortality study of nickel/chromium platers found increased lung cancer among male workers with some period of chrome bath work (SMR = 157; 95% CI, 113-214; $P < 0.01$).

Becker N. Cancer mortality among arc welders exposed to fumes containing chromium and nickel: Results of a third follow-up: 1989-1995. Journal of Occupational and Environmental Medicine 1999; 41: 294-303.

This cohort mortality study of arc welders exposed to fumes containing both chromium and nickel found increased mortality due to respiratory cancer (SMR = 121.5; 95% CI, 80.7-175.6).

Gibb HJ, Lees PSJ, Pinsky PF, Rooney BC. Lung cancer among workers in chromium chemical production. American Journal of Industrial Medicine 2000; 38: 115-126.

This cohort mortality study among workers in chromium chemical production found a dose-response relationship between lung cancer mortality and cumulative hexavalent chromium exposure. In the highest exposure category, the observed to expected ratio was 2.24.

Moulin JJ, Clavel T, Roy D, et al. Risk of lung cancer in workers producing stainless steel and metallic alloys. International Archives of Occupational and Environmental Medicine 2000; 73: 171-180.

This is a report of both a historical cohort mortality study and nested case-control study concerning lung cancer in workers producing stainless steel and metallic alloys. The cohort study found nonsignificantly increased mortality due to lung cancer (SMR = 1.19; 95% CI, 0.88-1.55). The case control study found a nonsignificant association between lung cancer and exposure to chromium and/or nickel (odds ratio = 1.18; 95% CI, 0.62-2.25).

Sorahan T, Harrington JM. Lung cancer in Yorkshire chrome platers, 1972-97. Occupational and Environmental Medicine 2000; 57: 385-389.

This cohort mortality study in chrome platers found significantly increased mortality due to lung cancer
(SMR = 185; $P < 0.001$).

Steenland K. Ten-year update on mortality among mild-steel welders. Scandinavian Journal of Work, Environment & Health 2002; 28: 163-167.

This cohort mortality study of mild-steel welders found significantly increased mortality due to lung cancer (SMR = 1.46; 95% CI, 1.20-1.76) for welders.

Luippold RS, Mundt KA, Dell LD, Birk T. Low-level hexavalent chromium exposure and rate of mortality among US chromate production employees. Journal of Occupational and Environmental Medicine 2005; 47: 381-385.

This cohort mortality study of chromate production employees did not find increased mortality due to lung cancer.

Birk T, Mundt KA, Dell LD, et al. Lung cancer mortality in the German chromate industry, 1958 to 1998. Journal of Occupational and Environmental Medicine 2006; 48: 426-433.

This cohort mortality study of chromate industry workers found increased mortality due to lung cancer (SMR = 1.48; 95% CI, 0.93-2.25), and significantly increased mortality due to lung cancer in the highest exposure category
(SMR = 2.09; 95% CI, 1.08-3.65).

Hara T, Hoshuyama T, Takahashi K, et al. Cancer risk among Japanese chromium platers, 1976-2003. Scandinavian Journal of Work, Environment & Health 2010; 36: 216-221.

This cohort mortality study of chromium platers found significantly increased mortality due to lung cancer
(SMR = 1.59; 95% CI, 1.01-2.38).

Gibb HJ, Lees PS, Wang J, O'Leary KG. Extended followup of a cohort of chromium production workers. American Journal of Industrial Medicine 2015: 58: 905-913.

This report of an extended follow-up of a cohort mortality study of chromium production workers found significantly increased mortality due to respiratory system cancer (trachea, bronchus, and lung) (SMR = 1.63; 95% CI, 1.42-1.86).

Case-control Studies

Droste JHJ, Weyler JJ, Van Meerbeeck JP, et al. Occupational risk factors of lung cancer: A hospital-based case-control study. Occupational and Environmental Medicine 1999; 56: 322-327.

This case-control study of occupational risk factors of lung cancer found a significant association between exposure to chromium and lung cancer (adjusted odds ratio = 1.4; 95% CI, 1.0-1.9).

Beveridge R, Pintos J, Parent M-E, et al. Lung cancer risk associated with occupational exposure to nickel, chromium VI, and cadmium in two population-based case-control studies in Montreal. American Journal of Industrial Medicine 2010; 53: 476-485.

This report of two case-control studies found a significant association between lung cancer and exposure to hexavalent chromium (odds ratio = 2.4; 95% CI, 1.2-4.8).

Meta-analyses and Systematic Reviews

Stern RM. Assessment of risk of lung cancer for welders. Archives of Environmental Health 1983; 38: 148-155.

This study found that welders appear to have an excess risk for lung cancer, approximately 30% above that of the non-welding population, which the authors determined could not be completely accounted for by tobacco use or by standard exposure.

Sjögren B, Hansen KS, Kjuus H, Persson P-G. Exposure to stainless steel welding fumes and lung cancer: A meta-analysis. Occupational and Environmental Medicine 1994; 51: 335-336.

This meta-analysis of exposure to stainless steel welding fumes and lung cancer found a significantly increased pooled relative risk estimate (1.94; 95% CI, 1.28-2.93). The study took into account both asbestos exposure and smoking habits.

Park RM, Bena JF, Stayner LT, et al. Hexavalent chromium and lung cancer in the chromate industry: A quantitative risk assessment. Risk Analysis 2004; 24: 1099-1108.

This quantitative risk assessment on hexavalent chromium and lung cancer in the chromate industry found that the estimated rate ratio of 1 mg/m^3-year of cumulative exposure to hexavalent chromium, with a lag of 5 years, was 2.44 (95% CI, 1.54-3.83).

van Wijngaarden E, Mundt KA, Luippold RS. Evaluation of the exposure-response relationship of lung cancer mortality and occupational exposure to hexavalent chromium based on published epidemiological data. Nonlinearity in Biology, Toxicology, and Medicine 2004; 2: 27-34.

This assessment of the exposure-response relationship of lung cancer mortality and occupational exposure to hexavalent chromium concluded that a linear dose-response describes the relationship between hexavalent chromium and lung cancer reasonably well, and therefore, their analyses do not necessarily support the threshold hypothesis for lung carcinogenicity of hexavalent chromium.

Cole P, Rodu B. Epidemiologic studies of chrome and cancer mortality: A series of meta-analyses. Regulatory Toxicology and Pharmacology 2005; 43: 225-231.

This report on a series of meta-analyses of studies pertaining to hexavalent chromium compounds and cancer mortality found significantly increased mortality due to lung cancer (SMR = 141; 95% CI, 135-147).

<u>Bioavailability and biologic mechanisms</u>:

According to the National Institute for Occupational Safety and Health (NIOSH), hexavalent chromium (Cr(VI)) is causally linked to lung cancer risk.[1] The American Lung Association specifically links Cr in coal ash to cancer risk.[2] Linda Evan's report from 2011,[3] citing data from the Electric Power Research Institute,[4] notes that coal ash leaches chromium in amounts that can greatly exceed EPA's threshold for hazardous waste at 5000 parts per billion (ppb), and that the chromium that leaches from coal ash is "nearly 100 percent [hexavalent] Cr(VI). The ratio of Cr levels in the TVA coal ash to Cr levels in background soil was 2.1,[5] indicating elevated levels of As in the TVA coal ash. The agencies found similar levels of chromium in coal ash with TVA, TDEC, and EPA finding a mean of 42, 25, and 28.2 mg/kg respectively.[10] The National Toxicology Program has specifically linked inhalation of Cr to lung cancer,[6] evidence also supports the carcinogenicity of Cr via ingestion. Based on toxicological, animal and epidemiologic evidence, IARC classifies Cr(VI) as group 1 carcinogen.[7]

According to Weiss et al (2008),[8] the particulate form of Cr(VI) dissolves slowly in vivo, leading to an extended exposure of lung cells. Hexavalent chromium is taken into the cell and broken down to Cr(V), Cr(IV), Cr(III), and reactive oxygen species. Cells thus treated show several types of DNA damage resulting from this reduction, including base modification, single-strand breaks, double-strand breaks, Cr-DNA adducts, DNA-Cr-DNA adducts, base pair stacking, and protein-Cr-DNA adducts. In turn, these damages lead to growth arrest, cytotoxicity, and apoptosis, as well as mutations leading to neoplastic transformation and ultimately tumorigenesis.[8,9]

References

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2. Toxic Air; The Case for Cleaning Up Coal-fired Power Plants, March 2011. http://www.lung.org/assets/documents/healthy-air/toxic-air-report.pdf

3. Evans L, Gottlieb B, Widawsky L, et al. EPA's Blind Spot. Hexavalent Chromium and Coal Ash: The Deadly Connection. February 1, 2011. http://www.psr.org/assets/pdfs/epas-blind-spot.pdf

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5. Ruhl L, Vengosh A, Dwyer GS, et al. Survey of the Potential Environmental and Health Impacts in the Immediate Aftermath of the Coal Ash Spill in Kingston, Tennessee. Environ. Sci. Technol. 2009, 43, 6326–6333.

6. National Toxicology Program. Hexavalent chromium. https://www.niehs.nih.gov/health/materials/hexavalent_chromium_508.pdf

7. IARC, Lyon, France. Arsenic, Metals, Fibres, and Dusts. Volume 100 C: A Review of Human Carcinogens, 2012. http://monographs.iarc.fr/ENG/Monographs/vol100C/index.php

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10. Tennessee Valley Authority (TVA), Document No. EPA-AO-030, TVA Kingston Fossil Fuel Plant Release Site, On-Scene Coordinator Report for the Time-Critical Removal Action, May 11, 2009 through December 2010, Harriman, Roane County, Tennessee.

Cadmium and Lung Cancer

Analysis of the following medical and scientific literature supports a causal association between exposure to cadmium in coal ash and occurrence of lung cancer, based on satisfaction of the following Bradford Hill Principles:

Strength
Consistency
Temporality
Biologic Gradient (Dose-response Relationship)
Biologic Plausibility

A positive association between cadmium and lung cancer has been observed in many epidemiologic studies over several decades among studies of different populations using several study designs, and controlling for a wide range of potentially confounding factors. In the cohort studies, exposure was measured prior to the measurement of the outcome (temporality), thus avoiding recall bias. Studies often showed positive dose-response associations. Several studies showed relative risk estimated in the moderate to strong range. Several biologically plausible mechanisms have been proposed, including those related to disturbances of DNA-repair and tumor-suppressor proteins, chromosomal damage and genomic instability, changes in DNA-methylation patterns, and deregulation of cell growth. Based on ample published literature, two meta-analyses have been performed concluding that there is an association between chromium and lung cancer.

Cohort Studies

Elinder C-G, Kjellstrom T, Hogstedt C, et al. Cancer mortality of cadmium workers. British Journal of Industrial Medicine 1985; 42: 651-655.

This study of cancer mortality among cadmium workers found significantly increased mortality due to lung cancer
(SMR = 121; *P* = 0.008).

Thun MJ, Schnorr TM, Smith AB, et al. Mortality among a cohort of U.S. cadmium production workers: An update. Journal of the National Cancer Institute 1985; 74: 325-333.

This updated report of a cohort mortality study of cadmium production workers found significantly increased mortality for lung cancer among those with 2 or more years of employment (SMR = 229; 95% CI, 131-371). This study also found evidence of a dose-response relationship: Among those in the lowest tertile of cumulative exposure to cadmium, the SMR was 53; among those in the middle tertile, the
SMR was 152; and among those in the highest tertile of cumulative cadmium exposure, the SMR was 280.

Kjuus H, Andersen A, Langård S. Incidence of cancer among workers producing calcium carbide. British Journal of Industrial Medicine 1986; 43: 237-242.

This study of cancer incidence among workers producing calcium carbide found an increase in lung cancer among furnace and maintenance workers (standardized incidence ratio = 1.56).

Sorahan T. Mortality from lung cancer among a cohort of nickel cadmium battery workers: 1946-84. British Journal of Industrial Medicine 1987; 44: 803-809.

This cohort mortality study of a cohort of nickel cadmium battery workers found significantly increased mortality due to lung cancer among those first employed between 1947 and 1975 for the period between 30 to 40 years since employment (SMR = 250).

Kazantzis G, Lam T-H, Sullivan KR. Mortality of cadmium-exposed workers: A five-year update. Scandinavian Journal of Work, Environment & Health 1988; 14: 220-223.

This updated cohort mortality study of cadmium-exposed workers found significantly increased mortality due to lung cancer (SMR = 115; 95% CI, 101-129).

Stayner L, Smith R, Thun M, et al. A dose-response analysis and quantitative assessment of lung cancer risk and occupational cadmium exposure. Annals of Epidemiology 1992; 2: 177-194.

This study of lung cancer mortality among cadmium-exposed workers found significantly increased mortality among workers in the highest cadmium exposure group (SMR = 272; 95% CI, 123-513). This study also found a statistically significant dose-response relationship in almost all the regression models that were evaluated.

Sorahan T, Lister A. Gilthrope MS, Harrington JM. Mortality of copper cadmium alloy works with special reference to lung cancer and non-malignant diseases of the respiratory system, 1946-92. Occupational and Environmental Medicine 1995; 52: 804-812.

This cohort mortality study of copper cadmium alloy workers did not find overall increased mortality due to lung cancer.

Sorahan T, Lancashire RJ. Lung cancer mortality in a cohort of workers employed at a cadmium recovery plant in the United States: An analysis with detailed job histories. Occupational and Environmental Medicine 1997; 54: 194-201.

This study of lung cancer mortality in a cohort of workers at a cadmium recovery plant found a dose-response relationship between exposure to cadmium and lung cancer mortality. In the highest exposure group, the relative risk was 3.88 (95% CI, 1.04-14.46).

Sorahan T, Esmen NA. Lung cancer mortality in UK nickel-cadmium battery workers, 1947-2000. Occupational and Environmental Medicine 2004; 61: 108-116.

This updated report of a cohort mortality study of nickel-cadmium battery workers found increased mortality due to lung cancer (SMR = 111; 95% CI, 81-148).

Nawrot T, Plusquin M, Hogervorst J, et al. Environmental exposure to cadmium and risk of cancer: A prospective population-based study. Lancet Oncology 2006; 7: 119-126.

This prospective population-based study on environmental exposure to cadmium and risk of cancer found a significant association between lung cancer and urinary cadmium

levels; the adjusted hazard ratio for lung cancer was 1.70 (95% CI, 1.13-2.57; *P* = 0.011) for a doubling of 24-hour urinary cadmium excretion.

Jones SR, Atkin P, Holroyd C, et al. Lung cancer mortality at a UK tin smelter. Occupational Medicine 2007; 57: 238-245.

This cohort mortality study of workers at a tin smelter who had been exposed to cadmium as well as arsenic, lead, antimony, and polonium-210 did not find a significant association between lung cancer mortality and cumulative exposure to cadmium.

Adams SV, Passarelli MN, Newcomb PA. Cadmium exposure and cancer mortality in the Third National Health and Nutrition Examination Survey cohort. Occupational and Environmental Medicine 2012; 69: 153-156.

This study of cadmium exposure and cancer mortality based on the Third National Health and Nutrition Examination Survey (NHANES III) found that lung cancer mortality was associated with creatinine-corrected urinary cadmium concentrations. In men, the adjusted hazard ratio was 1.81 (95% CI, 1.49-2.21). In women, the adjusted hazard ratio was 1.21 (95% CI, 0.79-1.84).

García-Esquinas E, Pollan M, Tellez-Plaza M, et al. Cadmium exposure and cancer mortality in a prospective cohort: The Strong Heart Study. Environmental Health Perspectives 2014; 122: 363-370.

This prospective cancer mortality study among American Indians in Arizona, Oklahoma, North Dakota, and South Dakota, who had participated in the Strong Heart Study, found increased lung cancer mortality associated with urinary cadmium (hazard ratio = 2.27; 95% CI, 1.57-3.27).

Case-control Study

Beveridge R, Pintos J, Parent M-E, et al. Lung cancer risk associated with occupational exposure to nickel, chromium VI, and cadmium in two population-based case-control studies in Montreal. American Journal of Industrial Medicine 2010; 53: 476-485.

This report of two case-control studies found a significant association between lung cancer and exposure to cadmium (odds ratio = 4.7; 95% CI, 1.5-14.3).

Meta-Analysis

Chen C, Xun P, Nishijo M, He K. Cadmium exposure and risk of lung cancer: A meta-analysis of cohort and case-control studies among general and occupational populations. Journal of Exposure Science and Environmental Epidemiology 2016; 26: 437-444.

This meta-analysis of cadmium exposure and risk of lung cancer based on three general-population cohort studies, five occupational cohort studies, and three occupational case-control studies found that the weighted relative risk for lung cancer, comparing the highest and lowest category of cadmium exposure, in the general population was 1.42

(95% CI, 0.91-2.23), the weighted risk estimate for lung cancer in the occupational cohort studies was 0.68 (95% CI, 0.33-1.01), and the weighted risk estimate for lung cancer in the three occupational case-control studies was 1.61 (95% CI, 0.94-2.75).

Nawrot TS, Martens DS, Hara A, et al. Association of total cancer and lung cancer with environmental exposure to cadmium: the meta-analytical evidence. Cancer Causes Control. 2015 Sep;26(9):1281-8. doi: 10.1007/s10552-015-0621-5.

The meta-analysis included 20,459 participants from three prospective population studies. The average urinary cadmium concentration across populations ranged from 0.25 to 0.93 µg/g creatinine. The relative risk of total cancer, associated with a doubling of the urinary cadmium concentration, ranged across the different studies from 1.18 to 1.31, and the pooled relative risk was 1.22 (95% CI 1.13-1.31; $p < 0.0001$). For lung cancer, the the relative risk ranged from 1.21 to 1.70 for a doubling of the urinary cadmium concentration, while the pooled relative risk amounted to 1.68 (1.47-1.92; $p < 0.0001$). The authors conclude that the epidemiological evidence of the last decade consistently identifies low-level environmental exposure to cadmium as a risk factor for total cancer and lung cancer.

Bioavailability and biologic mechanisms:

According to IARC, there is *sufficient evidence* in humans (and in animals) for the carcinogenicity of cadmium and cadmium compounds.[1] Cadmium and cadmium compounds are *carcinogenic to humans (Group 1).* Cadmium and cadmium compounds cause cancer of the lung and other cancers, such as those of the kidney and prostate. Inhalation is the major route of cadmium exposure in occupational settings. Exposure to cadmium particulates lead to cadmium absorption in animals and humans. In occupational settings, cadmium and cadmium compounds, being non-volatile, exist in air as fine particulates. Animal studies[2] have shown that lung retention may be up to 20%, especially after short-term exposure.

According to IARC,[1] various cadmium compounds (cadmium chloride, cadmium oxide, cadmium oxide dust, cadmium oxide fumes, cadmium sulfide) induce lung tumors via inhalation in rats. Intratracheal administration of cadmium chloride and cadmium sulfide induces lung tumors in rats.[1] Absorbed cadmium is excreted very slowly.[3] In humans, half-life estimates are in the range of 7–16 years.[3,4]

The ratio of Cd levels in the TVA coal ash to Cd levels in background soil was 3.0,[5] indicating elevated levels of As in the TVA coal ash. Significantly higher levels were found by the EPA with a mean of 0.86 mg/kg.[8] Several mechanisms have been identified that potentially contribute to cadmium-induced carcinogenesis.[1,6] Direct binding to DNA appears to be of minor importance, and mutagenic responses are weak. Convincing evidence exists on disturbances of DNA-repair and tumor-suppressor proteins, which lead to chromosomal damage and genomic instability. Further reported effects include changes in DNA-methylation patterns as well as interactions with signal-transduction processes, which may contribute to the deregulation of cell growth.

However, it is not yet possible to assess the relative contributions of these latter mechanisms for cancer in humans. Nordberg (2006) noted that in the cadmium lung cancer association there may be both interaction and/or confounding by arsenic exposure,[7] but the overall association with cadmium appears to be both independent and strong.

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Fine Particulate Matter and Lung Cancer

Analysis of the following medical and scientific literature supports a causal association between exposure to lead in coal ash and occurrence of hypertension, based on satisfaction of the following Bradford Hill Principles:

Strength
Consistency
Temporality
Biologic Gradient (Dose-response Relationship)
Plausibility

A positive association between fine particulate matter and lung cancer has been observed in many epidemiologic studies over several decades among studies of different populations using several study designs, and controlling for a wide range of potentially confounding factors. In the cohort studies, exposure was measured prior to the measurement of the outcome (temporality), thus avoiding recall bias. Studies often showed positive dose-response associations. Several studies showed relative risk estimated in the moderate to strong range. The carcinogenic sequelae of lung inflammation are among the most salient biologic mechanisms. Based on ample published literature, two meta-analyses have been performed concluding that there is an association between fine particulate matter and lung cancer.

Cohort Studies

Dockery DW, Pope CA III, Xu X, et al. An association between air pollution and mortality in six U.S. cities. New England Journal of Medicine 1993; 329: 1753-1759.

This cohort study found, that for a difference in air-pollution level equal to that between the most polluted city and the least polluted city for fine particles, the adjusted rate ratio was 1.26 (95% CI, 1.08-1.47), a significant association.

Turner MC, Krewski D, Pope CA III, et al. Long-term ambient fine particulate matter air pollution and lung cancer in a large cohort of never-smokers. American Journal of Respiratory and Critical Care Medicine 2011; 184: 1374-1381.

This study of long-term ambient fine particulate matter air pollution and lung cancer in a large cohort of never-smokers found, for the 1990-2000 period, a fully adjusted hazard ratio of 1.27 (95% CI, 1.03-1.56), a significant association, and for the 1979-1983 period, a fully adjusted hazard ratio of 1.15 (95% CI, 0.99-1.35).

Lepeule J, Laden F, Dockery D, Schwartz J. Chronic exposure to fine particles and mortality: An extended follow-up of the Harvard Six Cities Study from 1974 to 2009. Environmental Health Perspectives 2012; 120: 965-970.

This report on an extended follow-up of the Harvard Six Cities Study from 1974 to 2009 found that chronic exposure to fine particles was significantly associated with lung cancer mortality – each 10 $\mu g/m^3$ in fine particulate matter was associated with a 37% increase in lung cancer mortality (95% CI, 7%-75%).

Cesaroni G, Badaloni C, Gariazzo C, et al. Long-term exposure to urban air pollution and mortality in a cohort of more than a million adult in Rome. Environmental Health Perspectives 2013; 121: 324-331.

This cohort mortality study of more than a million adults found that each 10 μg/m^3 increase in fine particulate matter was significantly associated with an adjusted hazard ratio of 1.05 (95% CI, 1.01-1.10).

Burnett RT, Pope CA III, Ezzati M, et al. An integrated risk function for estimating the global burden of disease attributable to ambient fine particulate matter exposure. Environmental Health Perspectives 2014; 122: 397-403.

This report on an integrated risk function for estimating the global burden of disease attributable to ambient fine particulate matter exposure projected a significant association between fine particulate matter and lung cancer (relative risk = 1.09; 95% CI, 1.06-1.12).

Turner MC, Cohen A, Jerrett M, et al. Interactions between cigarette smoking and fine particulate matter in the risk of lung cancer mortality in Cancer Prevention Study II. American Journal of Epidemiology 2014; 180: 1145-1149.

This cohort study found that relative excess risk of lung cancer mortality due to the interaction of cigarette smoking and fine particulate matter was 2.19 (95% CI, -0.10-4.83). Among never-smokers, there was a significant association between fine particulate matter and lung cancer mortality (hazard ratio = 1.41; 95% CI, 1.06-1.88, comparing those in the highest tertile with those in the lowest tertile). Among current smokers, there was a significant association between fine particulate matter and lung cancer mortality (hazard ratio = 16.48; 95% CI, 12.91-21.05, comparing those in the highest tertile with those in the lowest tertile).

Tomczak A, Miller AB, Weichenthal SA, et al. Long-term exposure to fine particulate matter air pollution and the risk of lung cancer among participants of the Canadian National Breast Screening Study. International Journal of Cancer 2016; 139: 1958-1966.

This cohort study found that, for each 10 μg/m^3, increase in fine particulate matter, there was a significantly increased risk of lung cancer (hazard ratio = 1.34; 95% CI, 1.10-1.65).

Gharivband L, Beeson WL, Shavlik D, et al. The association between ambient fine particulate matter and incidence adenocarcinoma subtype of lung cancer. Environmental Health 2017; 16:71 doi.10.1186/s12940-017-0268-7.

This cohort study found that, excluding individuals with prevalent non-melanoma skin cancer, each 10 μg/m^3 increment in fine particulate matter significantly increased the risk of lung cancer (hazard ratio = 1.62; 95% CI, 1.11-2.36). In addition, an analysis limited to subjects who spent more than 1 hour a day outside, found that each 10 μg/m^3 increment in fine particulate matter significantly increased the risk of lung cancer (hazard ratio = 1.55; 95% CI, 1.05-2.30).

Gharibvand L, Shavlik D, Ghamsary M, et al. The association between fine particulate air pollution and lung cancer incidence: Results from the AHSMOG-2 Study. Environmental Health Perspectives 2017; 125: 378-384.

This cohort study found that each 10 μg/m^3 increment in fine particulate matter significantly increased the risk of lung cancer (adjusted hazard ratio = 1.43; 95% CI, 1.11-1.84).

Pinault LL, Weichenthal S, Crouse DL, et al. Associations between fine particulate matter and mortality in the 2001 Canadian Census Health and Environment Cohort. Environmental Research 2017; 159: 406-415.

This cohort study found that each 10 μg/m^3 increase of fine particulate matter significantly increased the risk of lung cancer (fully adjusted hazard ratio = 1.158; 95% CI, 1.072-1.252).

Pun VC, Kazemparkouhi F, Manjourides J, Suh HH. Long-term $PM_{2.5}$ exposure and respiratory, cancer, and cardiovascular mortality in older US adults. American Journal of Epidemiology 2017; 186: 961-969.

This cohort mortality study found that each 10 μg/m^3 increase in 12-month moving average of fine particulate matter in the Behavioral Risk Factor Surveillance System-adjusted model significantly increased the risk of lung cancer (relative risk = 1.149; 95% CI, 1.116-1.183).

Yin P, Brauer M, Cohen A, et al. Long-term fine particulate matter exposure and nonaccidental and cause-specific mortality in a large national cohort of Chinese men. Environmental Health Perspectives 2017; 125:117002.

This study found a significant increased risk of lung cancer for each 10 μg/m^3 in fine particulate matter (mortality hazard ratio = 1.09; 95% CI, 1.08-1.09).

Meta-Analyses:

Huang F, Pan B, Wu J, et al. Relationship between exposure to PM2.5 and lung cancer incidence and mortality: A meta-analysis. Oncotarget 2017;8:43322-43331.

This meta-analysis examined the relationship between exposure to PM2.5 and lung cancer incidence and mortality in 17 studies. The meta-estimate for lung cancer risk associated with PM2.5 was 1.11 for mortality (95% CI: 1.05, 1.18) and 1.08 (95% CI: 1.03, 1.12) for incidence. In subgroup analyses of males and females, the meta-estimate for lung cancer mortality associated with PM2.5 was greater for males [1.26 (95% CI: 1.15, 1.40)] than for females [1.17 (95% CI: 0.98, 1.39)]. The meta-estimate for lung cancer incidence associated with PM2.5 was greater for males [1.23 (95% CI: 0.83, 1.81)] than for females [1.15 (95% CI: 1.12, 1.18)].

Hamra GB, Guha N, Cohen A, et al. Outdoor particulate matter exposure and lung cancer: a systematic review and meta-analysis. Environ Health Perspect 2014: 122:906–911; http://dx.doi.org/10.1289/ehp.1408092

The meta-relative risk for lung cancer associated with PM2.5 was 1.09 (95% CI: 1.04, 1.14). The meta-relative risk of lung cancer associated with PM10 was similar, but less precise: 1.08 (95% CI: 1.00, 1.17). Estimates were robust to restriction to studies that considered potential confounders, as well as subanalyses by exposure assessment method. Analyses by smoking status showed that lung cancer risk associated with PM2.5 was greatest for former smokers [1.44 (95% CI: 1.04, 2.01)], followed by never-smokers [1.18 (95% CI: 1.00, 1.39)], and then current smokers [1.06 (95% CI: 0.97, 1.15)]. In addition, meta-estimates for adenocarcinoma associated with PM2.5 and PM10 were 1.40 (95% CI: 1.07, 1.83) and 1.29 (95% CI: 1.02, 1.63), respectively.

Bioavailability and biologic mechanisms:

In October 2013, the International Agency for Research on Cancer (IARC) classified particulate matter (PM) from outdoor air pollution as carcinogenic to humans and a cause of lung cancer.[1]

PM2.5 includes a higher proportion of mutagenic species,[2] many of which are products of combustion. Further, smaller particles penetrate more deeply into the lung and are more likely to be retained.[3,4] Thus, PM2.5 is generally believed to be most relevant to health effects, including cancer. The Centers for Disease Control and Prevention has also concluded that inhalation of particulate matter is causally related to lung cancer risk.[5] According to the American Lung Association, particulates specifically in Coal Ash increases risk of lung cancer and other respiratory and non-respiratory outcomes.[6] The American Lung Association also cited evidence, and fully endorsed the conclusion, that even short-term exposure to particulates can be harmful to health in many ways. In March 2011, the American Lung Association released the report, "Toxic Air: The Case for Cleaning Up Coal-fired Power Plants," on the hazardous air pollutants emitted from power plants. Key findings from the report included:

- Coal-fired power plants produce more hazardous air pollution in the United States than any other industrial pollution sources;
- More than 400 coal-fired power plants located in 46 states across the country release in excess of 386,000 tons of hazardous air pollutants into the atmosphere each year;
- Particulate matter pollution from power plants is estimated to kill approximately 13,000 people a year.

Mechanisms:

One of the key mechanisms is lung inflammation, which has been demonstrated in independent studies.[6] Silica, which is present in coal ash, is also a cited mechanism.[7,8]

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Ionizing Radiation and Leukemia

Analysis of the following medical and scientific literature supports a causal association between exposure to ionizing radiation in coal ash and occurrence of leukemia, based on satisfaction of the following Bradford Hill Principles:

Strength
Consistency
Temporality
Biologic Gradient (Dose-response Relationship)
Plausibility
Coherence

A positive association between ionizing radiation and leukemia risk has been observed in many epidemiologic studies over several decades among studies of different populations using several study designs, and controlling for a wide range of potentially confounding factors. Although the number of prospective analyses is limited, follow-up of exposed individuals (for example, those who were exposed to ionizing radiation during WWII, avoids the issue of recall bias. Large doses of radiation are not necessary for the association. For example, a review of the literature concluded: "The prevailing opinion is that with increasing dose the relationship should be considered linear without a threshold." Studies often showed positive dose-response associations. Several studies showed relative risk estimated in the moderate to strong range. Radiation-induced chromosomal rearrangements are a plausible biologic mechanism. Based on ample published literature, several meta-analyses and reviews of the literature have been performed concluding that there is an association between ionizing radiation and leukemia.

Case-control Studies

Flodin U, Andersson L, Anjou C-G, et al. A case-referent study on acute myeloid leukemia, background radiation and exposure to solvents and other agents. Scandinavian Journal of Work, Environment & Health 1981; 7: 169-178.

This case-control study found that, especially between ages 20 and 40 and to some extent between ages 50 and 69 background radiation seemed to increase the occurrence of acute myeloid leukemia, with a trend of an exposure-effect relationship.

Flodin U, Fredriksson M, Persson B, Axelson O. Acute myeloid leukemia and background radiation in an expanded case-referent study. Archives of Environmental Health 1990; 45: 364-366.

This case-control study, based on 86 cases of acute myeloid leukemia (AML) and 172 referents, found an association between (a) time spent in concrete buildings at home and work and (b) leukemia morbidity. The study also found that extensive x-ray examinations occurring more than 5 years before diagnosis of AML were more common among cases than referents.

Systematic Review and Meta-analyses

Raaschou-Nielsen O. Indoor radon and childhood leukaemia. Radiation Protection Dosimetry 2008; 132: 175-181.

This publication, which summarized epidemiologic studies on domestic radon exposure and childhood leukemia risk stated that, based on 12 ecological studies, there is a consistent pattern of higher incidence and mortality rates for childhood leukemia in those areas that have higher average concentrations of indoor radon.

Tong J, Qin L, Cao Y, et al. Environmental radon exposure and childhood leukemia. Journal of Toxicology and Environmental Health, Part B 2012; 15: 332-347.

This meta-analysis found an increased risk of childhood leukemia that was induced by indoor exposure to radon for overall leukemia and also for acute lymphoblastic leukemia (ALL).

Ecological Study

Edling C, Comb P, Axelson O, Flodin U. Effects of low-dose radiation: A correlation study. Scandinavian Journal of Work, Environment & Health 1982; 8 (suppl 1): 59-64.

This ecological study found a significant correlation
(R = 3.6) between leukemia in males and low-dose radiation (*P* = 0.04).

Review Articles

Kellerer AM. Risk estimates for radiation-induced cancer: The epidemiological evidence. Radiation and Environmental Biophysics 2000; 39: 17-24.

This review article provides an overview of the epidemiologic evidence for radiation-induced cancer, including increases in mortality from both solid tumors and leukemia after the atomic bomb attacks on Hiroshima and Nagasaki.

Finch SC. Radiation-induced leukemia: Lesson from history. Best Practice & Research Clinical Haematology 2007; 20: 109-118.

This review article on radiation-induced leukemia concluded the following:

- "Quantitative dose-response relationships now have been established for leukemia for most types of ionizing radiation. The prevailing opinion is that with increasing dose the relationship should be considered linear without a threshold.
- In general, the younger the age of exposure, the greater susceptibility to radiation-induced leukemia.
- Fractionated doses of radiation, such as we get throughout our lifetime, are less leukemogenic than in an equivalent single large dose.
- CLL [chronic lymphocytic leukemia, now considered a form of non-Hodgkin lymphoma] has not been linked to radiation exposure.

- A latent period of 1 to 2 years exists between the occurrence of a major radiation exposure event and the development of leukemia.
- The extent of radiation-induced chromosomal rearrangements appears to play an important role in the induction of leukemia and other tumors."

Kheifets L, Swanson J, Yuan Y, et al. Comparative analyses of studies of childhood leukemia and magnetic fields, radon and gamma radiation. Journal of Radiological Protection 2017; 37: 359-491.

This paper, which reported on comparative analyses of studies of childhood leukemia and several risk factors (including radon exposure), found that, among 6 studies that analyzed data on leukemia and radon exposure, only 3 of the studies showed elevations in relative risk (from 1.1 to 1.3) and none of these elevations were statistically significant.

Bioavailability and biologic mechanisms:

Radium isotopes and lead-210 occur naturally in coal as chemical by-products of its uranium and thorium content. Levels of radioactivity in coal ash can be several times higher than in normal soil and is considered one of the human health risks posed by coal ash.[1,2] When the coal is burned, the radium isotopes become concentrated in the coal ash residues, and the lead-210 becomes chemically volatile and reattaches itself to tiny particles of fly ash, which causes additional enrichment of radioactivity in the fly ash.[1]

Levels of radium isotopes and other radionuclides were found in the Kingston coal ash by Ruhl and Vengosh[5] and by TVA and TDEC.[6] TDEC also measured gross alpha and beta emitters.[6]

For leukemia, with moderate or even low doses of ionizing radiation, the minimum time period between the radiation exposure and the appearance of disease (latency period) is 2 years.[3] In an analysis of the International Nuclear Workers Study (INWORKS),[4] investigators looked specifically at development of hematologic malignancies among workers from France, the United Kingdom, and the United States who were exposed to low-dose protracted or intermittent radiation. According to the findings, even low accrued doses of radiation (<5 mGy) had an excess risk of leukemia-related mortality, suggesting that the potential threshold below which radiation is harmless should be very low.

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Arsenic and Non-melanoma Skin Cancer

Analysis of the following medical and scientific literature supports a causal association between exposure to arsenic in coal ash and occurrence of non-melanoma skin cancer, based on satisfaction of the following Bradford Hill Principles:

Strength
Consistency
Temporality
Plausibility

A positive association between arsenic and non-melanoma skin cancer has been observed in many epidemiologic studies over several decades among studies of different populations using several study designs, and controlling for a wide range of potentially confounding factors. However, studies of arsenic inhalation and skin cancer have not been entirely consistent in their results. There is a dearth of prospective, i.e., cohort studies. However, several of the case-control studies did not rely solely on the participants' recollections of exposure, providing some reassurance of temporality (the exposure preceded the outcome). Studies often showed positive dose-response associations. Several studies showed relative risk estimated in the moderate to strong range. Inefficient methylation has been noted to be a plausible biologic mechanism. Based on ample published literature, the Canadian Cancer Society lists arsenic as a risk factor for non-melanoma skin cancer.

Case-Control Studies

Yu R, Hsu K-H, Chen C-J, et al. Arsenic methylation capacity and skin cancer. Cancer Epidemiol Biomark Prev 2000;9:1259-1262.

This case-control study found cases had higher percentage of InAs, percentage of MMA, and MMA:DMA ratio, and lower percentage of DMA than matched controls. Subjects with a higher percentage of MMA had a stronger tendency to develop arsenic-associated skin lesions than individuals having a lower percentage of MMA, with an OR as high as 5.5. The association was not confounded by other variables such as gender, age, hepatitis B surface antigen, smoking, alcohol consumption, or tea intake.

Surdu S, Fitzgerald EF, Bloom MS, et al. Occupational exposure to arsenic and risk of nonmelanoma skin cancer in a multinational European study. Int J Cancer. 2013 Nov;133(9):2182-91. doi: 10.1002/ijc.28216..

This case-control study assessed airborne arsenic exposures at the workplace in relation to nonmelanoma skin cancer (NMSC). The study sample consists of 618 incident cases of NMSC and 527 hospital-based controls aged 30-79 years from Hungary, Romania and Slovakia. No significant association between arsenic exposure in the workplace and NMSC was detected, although an increased adjusted odd ratio was observed for participants with higher cumulative lifetime workplace exposure to arsenic in dust and fumes compared to referents [odds ratios (OR) = 1.94, 95% confidence interval (CI) = 0.76-4.95]. There was evidence for modification of the workplace arsenic-NMSC

association by work-related sunlight exposure, such that workplace coexposure to arsenic and sunlight may pose an increased risk of NMSC.

Chen C-J, Wu M-M, Lee S-S, et al. Atherogenicity and carcinogenicity of high-arsenic artesian well water: Multiple risk factors and related malignant neoplasms of blackfoot disease. Arteriosclerosis 1988; 8: 452-460.

This case-control study in an area with high arsenic concentrations in artesian well water found significantly increased mortality due to skin cancer (SMR based on residents in the blackfoot disease-endemic area = 451).

Karagas MR, Stukel TA, Morris JS, et al. Skin cancer risk in relation to toenail arsenic concentrations in a US population-based case-control study. American Journal of Epidemiology 2001; 153: 559-565.

This case-control study which examined the relationship between skin cancer risk and toenail arsenic concentrations found that squamous cell carcinoma and basal cell carcinoma did not appear to be elevated at the toenail arsenic concentrations detected in study subjects, but the authors could not exclude the possibility of a dose-related increase at the highest level of exposure.

Pesch B, Ranft U, Jakubis P, et al. Environmental arsenic exposure from a coal-burning power plant as a potential risk factor for nonmelanoma skin carcinoma: Results from a case-control study in the District of Prievidza, Slovakia. American Journal of Epidemiology 2002; 155: 798-809.

This case-control study in a district of Slovakia found a significant excess of nonmelanoma skin cancer risk for environmental arsenic exposure. Among those in the highest exposure category, the odds ratio was 1.90 (95% CI, 1.39-2.60).

Chen Y-C, Guo YL, Su HJ, et al. Arsenic methylation and skin cancer risk in southwestern Taiwan. Journal of Occupational and Environmental Medicine 2003; 45: 241-248.

This case-control study found that males in all strata of arsenic exposure and methylation ability had a higher risk of skin cancer than women. It also found that subjects with low secondary arsenic methylation and high cumulative arsenic exposure had a substantially increased risk of skin cancer.

Rosales-Castillo JA, Acosta-Saavedra LC, Torres R, et al. Arsenic exposure and human papillomavirus response in non-melanoma skin cancer Mexican patients: A pilot study. International Archives of Occupational and Environmental Health 2004; 77: 418-423.

This case-control study found, both among those negative and those positive for human papilloma virus (HPV), a significant association between arsenic exposure and nonmelanoma skin cancer. Among those negative for HPV, the odds ratio was 4.53 (95% CI, 0.63-32.76). Among those positive for HPV, the odds ratio was 16.50 (95% CI, 2.97-91.75).

Mitropoulos P, Norman R. Occupational nonsolar risk factors of squamous cell carcinoma of the skin: A population-based case-controlled study. Dermatology Online Journal 2005; 11:5.

This case-control study found an association between exposure to arsenic and squamous cell carcinoma of the skin (odds ratio = 4.21; 95% CI, 0.40-43.9).

Leonardi G, Vahter M, Clemens F, et al. Inorganic arsenic and basal cell carcinoma in areas of Hungary, Romania, and Slovakia: A case-control study. Environmental Health Perspectives 2012; 120: 721-726.

This case-control study in areas of Hungary, Romania, and Slovakia found that basal cell carcinoma was positively associated with three indices of inorganic arsenic exposure.

Gilbert-Diamond D, Li Z, Perry AE, et al. A population-based case-control study of urinary arsenic species and squamous cell carcinoma in New Hampshire, USA. Environmental Health Perspectives 2013; 121: 1154-1160.

This case-control study found a significant association between squamous cell carcinoma of the skin and arsenic exposure (odds ratio = 1.37; 95% CI, 1.04-1.80).

Cross-Sectional Studies

Baastrup R, Sørensen M, Balstrøm T, et al. Arsenic in drinking-water and risk for cancer in Denmark. Environmental Health Perspectives 2008; 116: 231-237.

This cross-sectional study of 57,053 persons in the Copenhagen and Aarhus areas of Denmark did not find an increased incidence rate ratio for non-melanoma skin cancer in association with arsenic exposure.

Hsueh Y-M, Chiou H-Y, Huang Y-L, et al. Serum β-carotene level, arsenic methylation capability, and incidence of skin cancer. Cancer Epidemiology, Biomarkers & Prevention 1997; 6: 589-596.

This cross-sectional study found an elevated proportion of MMA of total urinary arsenic associated with an increased risk of skin cancer.

Ecologic Studies

Tseng WP, Chu HM, How SW, et al. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. Journal of the National Cancer Institute 1968; 40: 453-463.

This ecologic study found that the prevalence rate for skin cancer demonstrated an ascending gradient according to arsenic content of well water –- that is, the higher the arsenic content, the more patients with skin cancer.

Chen C-J, Chuang Y-C, Lin T-M, Wu H-Y. Malignant neoplasms among residents of a blackfoot disease-endemic area in Taiwan: High-arsenic artesian well water and cancers. Cancer Research 1985; 45: 5895-5899.

Blackfoot-disease is an endemic peripheral vascular disorder confined to limited areas of Taiwan and other countries where there are high concentrations of arsenic in well

water. This study found significantly increased rates of skin cancer mortality in a blackfoot-disease endemic area in Taiwan: among males, the SMR was 534 (95% CI, 379-689); among females, the SMR was 652 (95% CI, 469-835).

Chen C-J, Wang C-J. Ecological correlation between arsenic level in well water and age-adjusted mortality from malignant neoplasms. Cancer Research 1990; 50: 5470-5474.

This ecologic study of arsenic level in well water and age-adjusted mortality from various cancers found a significant association between the arsenic level in well water and age-adjusted mortality for skin cancer.

Guo H-R, Yu H-S, Hu H, Monson RR. Arsenic in drinking water and skin cancers: Cell-type specificity (Taiwan, R.O.C.). Cancer Causes and Control 2001; 12: 909-916.

This ecological study performed in an area where there were high concentrations of arsenic in drinking water found that arsenic levels above 0.64 mg/L were associated with increased risk for basal cell carcinoma in men and with squamous cell carcinoma of the skin in both men and women.

Bencko V, Rames J, Fabiánová E, et al. Ecological and human health risk aspects of burning arsenic-rich coal. Environmental Geochemistry and Health 2009; 31: 239-243.

This ecologic study found a positive correlation between human cumulative exposure to arsenic from the burning of coal with high arsenic content and the incidence of non-melanoma skin cancer.

Cheng P-S, Weng S-F, Chiang C-H, Lai F-J. Relationship between arsenic-containing drinking water and skin cancers in the arseniasis endemic areas in Taiwan. Journal of Dermatology 2016; 43: 181-186.

This ecological study found that incidence rates, in areas with high arsenic concentrations in drinking water, for squamous cell carcinoma of the skin were 4 to 6 times higher and that incidence rates for basal cell carcinoma were 3 to 4 times higher than the rest of Taiwan.

Consensus group opinions:

The Canadian Cancer Society lists arsenic as a risk factor for non-melanoma skin cancer.[1]

Biologic mechanisms:

Inefficient methylation, as indicated by low urinary excretion of DMA and high urinary excretion of MA, was associated with an increased risk of NMSC in populations consuming drinking water highly contaminated by arsenic.[2,3] This mechanism may not apply to low levels of arsenic exposure.

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3. Chen Y-C, Guo YL, Su HJ, et al. Arsenic methylation and skin cancer risk in southwestern Taiwan. Journal of Occupational and Environmental Medicine 2003; 45: 241-248.

Arsenic and Peripheral Neuropathy

Analysis of the following medical and scientific literature supports a causal association between exposure to arsenic in coal ash and occurrence of peripheral neuropathy, based on satisfaction of the following Bradford Hill Principles:

Strength
Consistency
Temporality
Plausibility

A positive association between arsenic and peripheral neuropathy has been observed in many epidemiologic studies over several decades among studies of different populations using several study designs, and controlling for a wide range of potentially confounding factors. There has been a dearth of prospective analyses. However, biologic measurements of arsenic have often been used, where studies have not relied solely on participants' recall of exposure, thereby limiting the potential for recall bias. Studies often showed positive dose-response associations. Several studies showed relative risk estimated in the moderate to strong range. The inhibition of neurite outgrowth and demyelination have been cited as plausible biologic mechanisms. Based on ample published literature, a review article on arsenic neurotoxicity stated: "The most frequent neurological manifestation by As [arsenic] is peripheral neuropathy that may last for several years or even life-long."

Case-Control Study

Sińczuk-Walczak H, Janasik BM, Trzcinka-Ochocka M, et al. Neurological and neurophysiological examinations of workers exposed to arsenic levels exceeding hygiene standards. International Journal of Occupational Medicine and Environmental Health 2014; 27: 1013-1025.

This case-control study demonstrated that peripheral neuropathy was manifested in arsenic-exposed workers in a copper smelting factory by extremity fatigue (29%), extremity pain (33%), paresthesias in the lower extremities (33%), and by neuropathy-type mini-symptoms (24%). Significant findings in these workers compared to a control group of non-exposed workers included muscular fatigue ($P = 0.019$), extremity pains ($P = 0.010$), and paresthesias ($P = 0.010$).

Cross-Sectional Studies

Gerr F, Letz R, Ryan PB, Green RC. Neurological effects of environmental exposure to arsenic in dust and soil among humans. NeuroToxicology 2000; 21: 475-488.

This cross-sectional study of people exposed environmentally to arsenic in dust and soil found that 13 (15.3%) of the exposed subjects met the case definition for peripheral neuropathy compared with 4 (3.4%) of the unexposed subjects (odds ratio = 5.1; $P = 0.004$).

Hafeman DM, Ahsan H, Louis ED, et al. Association between arsenic exposure and a measure of subclinical sensory neuropathy in Bangladesh. Journal of Occupational and Environmental Medicine 2005; 47: 778-784.

This cross-sectional study found that both cumulative arsenic index and urinary arsenic were both significantly associated with an elevated toe vibration threshold ($P = 0.02$ and $P = 0.009$, respectively) after adjustment for age and gender.

Tseng H-P, Wang Y-H, Wu M-W, et al. Association between chronic exposure to arsenic and slow nerve conduction velocity among adolescents in Taiwan. Journal of Health, Population and Nutrition 2006; 24: 182-189.

This cross-sectional study found a significant association between chronic exposure to arsenic and slow nerve conduction velocity among adolescents (odds ratio = 2.9; 95% CI, 1.1-1.75), after adjusting for gender and height.

Otto D, Xia Y, Li Y, et al. Neurosensory effects of chronic human exposure to arsenic associated with body burden and environmental measures. Human & Experimental Toxicology 2007; 26: 169-177.

This cross-sectional study of 3,020 residents, whose well water was contaminated with arsenic, found significant associations of pinprick scores and vibration thresholds with all measures of arsenic exposure.

Parvez F, Wasserman GA, Factor-Litvak P, et al. Arsenic exposure and motor function among children in Bangladesh. Environmental Health Perspectives 2011; 119: 1665-1670.

This cross-sectional study found that three measures of arsenic exposure (drinking water arsenic concentration, urinary arsenic concentration, and toenail arsenic concentration) were all inversely associated with motor function scores.

Paul S, Das N, Bhattacharjee P, et al. Arsenic-induced toxicity and carcinogenicity: A two-wave cross-sectional study in arsenicosis individuals in West Bengal, India. Journal of Exposure Science and Environmental Epidemiology 2013; 23: 156-162.

This is a cross-sectional study of 189 people with arsenicosis (manifestations of arsenic poisoning) and 171 unexposed individuals who were studied at two points in time (2005-2006 and 2010-2011) between which the concentration of arsenic in their drinking water was decreased. Despite this reduction in their ongoing exposure to arsenic, they nevertheless experienced over this time period a significant increase in the incidence of peripheral neuropathy, conjunctivitis, and respiratory distress. The odds ratio for peripheral neuropathy rose from 9.08 (95% CI, 3.48-23.72) during the 2005-2006 period to 18.48 (95% CI, 7.75-44.06) during the 2010-2011 period.

Case Series and Case Report

Heyman A, Pfeiffer JB, Willett RW, Taylor HM. Peripheral neuropathy caused by arsenical intoxication: A study of 41 cases with observations on the effects of BAL (2,3 dimercapto-propanol). New England Journal of Medicine 1956; 254: 401-408.

This is a report of 41 people with peripheral neuropathy caused by arsenical intoxication.

Mukherjee SC, Rahman MM, Chowdhury UK, et al. Neuropathy in arsenic toxicity from groundwater arsenic contamination in West Bengal, India. Journal of Environmental Science and Health 2003; A38: 165-183.

In this case series of 451 patients who developed arsenic toxicity from groundwater arsenic contamination in West Bengal, India, found that peripheral neuropathy was the predominant neurological complication affecting a total of 187 patients. The authors excluded other possible causes and alternative explanations for the neuropathy.

Mathew L, Vale A, Adcock JE. Arsenical peripheral neuropathy. Practical Neurology 2010; 10: 34-38.

This is a case report of a 49-year-old man who developed arsenical peripheral neuropathy, demonstrated by severe predominantly axonal large fiber sensorimotor neuropathy and evidence of this neuropathy on sural nerve biopsy.

Review Article

Ratnaike RN. Acute and chronic arsenic toxicity. Postgraduate Medical Journal 2003; 79: 391-396.

This review article stated that the neurological system is the major target of toxic effects of several metals, including arsenic. The author stated that the neuropathy is initially sensory, with a glove-and-stocking anesthesia. The author also stated that the most frequent finding is a peripheral neuropathy mimicking Guillain-Barré syndrome with similar electromyographic findings.

Vahidnia A, van der Voet GB, de Wolff FA. Arsenic neurotoxicity: A review. Human & Experimental Toxicology 2007; 26: 823-832.

This review article on arsenic neurotoxicity stated: “The most frequent neurological manifestation by As [arsenic] is peripheral neuropathy that may last for several years or even life-long.”

Biological mechanisms:

Biologic mechanisms have not been extensively studied. Arsenic produces a peripheral neuropathy characterized by axonal degeneration in humans. Using an in vitro model system of dorsal root ganglion neurons and morphometry of neurite outgrowth and myelination, an early study by Windebank[1] demonstrated that arsenic produced 50% inhibition of neurite outgrowth at 9.6 X 10(-6) M. Murphy et al[2] and Seppäläinen[3] analyzed the course of arsenic neuropathy and concluded that axonal lesions predominated in the early stage and demyelinated changes predominated in the later stage as secondary to the neurogenic process.

References

1. Windebank AJ. Specific inhibition of myelination by lead in vitro; comparison with arsenic, thallium, and mercury. Exp Neurol. 1986 Oct;94(1):203-12.

2. Murphy MJ, Lyon LW, Taylor JW. Subacute arsenic neuropathy: Clinical and electrophysiological observations. J Neurol Neurosurg Psychiatry. 1981;44:896–901, http://dx.doi.org/ 10.1136/jnnp.44.10.896.

3. Seppäläinen AM. Neurophysiological approaches to the detection of early neurotoxicity in humans. Crit Rev Toxicol. 1988;18(4):245–98, http://dx.doi.org/10.3109/10408448 809037468.

Lead and Peripheral Neuropathy

Analysis of the following medical and scientific literature supports a causal association between exposure to lead in coal ash and occurrence of peripheral neuropathy, based on satisfaction of the following Bradford Hill Principles:

Strength
Consistency
Temporality
Plausibility

A positive association between lead and peripheral neuropathy has been observed in many epidemiologic studies among studies over several decades of different populations using at least two observational study designs, controlling for a wide range of potentially confounding factors. In the cohort studies, exposure was measured prior to the measurement of the outcome (temporality), thus avoiding recall bias. Studies often showed positive dose-response associations. Several studies showed relative risk estimated in the moderate to strong range. Lead deposition in, and consequent direct injury to, Schwann cells giving rise to demyelination is a cited plausible biologic mechanism.

Cohort Studies

Araki S, Murata K, Uchida E, et al. Radial and median nerve conduction velocities in workers exposed to lead, copper, and zinc: A follow-up study for 2 years. Environmental Research 1993; 61: 308-316.

This cohort study reported on maximal motor and sensory conduction velocities in the distal radial and median nerve in 19 gun-metal foundry workers with asymptomatic increased absorption of lead, zinc, and copper. The two major findings of the study were (a) radial and median nerve conduction velocities were significantly slowed in these workers, and (b) indicators of lead absorption were inversely related to radial nerve conduction velocities.

Chia S-E, Chia K-S, Chia H-P, et al. Three-year follow-up of serial nerve conduction among lead-exposed workers. Scandinavian Journal of Work, Environment & Health 1996; 22: 374-380.

This cohort study followed, at 6-month intervals for 3 years, 72 lead battery manufacturing factory workers. At each follow-up visit, blood lead level was determined and nerve conduction tests were performed. There were 82 unexposed subjects who served as referents. In the more heavily exposed workers (40 µg/dL or higher blood lead level), the median motor nerve conduction velocity, median distal latency, median amplitude, ulnar motor conduction velocity, and ulnar amplitude were significantly correlated with blood lead level.

Yokoyama K, Araki S, Aono H, Murata K. Calcium disodium ethylenediaminetetraacetate-chelated lead as a predictor for subclinical lead neurotoxicity: Follow-up study on gun-metal

foundry workers. International Archives of Occupational and Environmental Health 1998; 71: 459-464.

In this cohort study of 17 male gun-metal foundry workers who conduction velocities in large myelinated fibers of the sensory median nerve were measured twice at 1-year intervals, results indicated that yearly changes in conduction velocities of faster fibers were significantly correlated with the corresponding change in mobilization yield of lead in urine by calcium disodium ethylenediamine-tetraacetate (CaEDTA).

Chuang H-Y, Schwartz J, Tsai S-Y, et al. Vibration perception thresholds in workers with long term exposure to lead. Occupational and Environmental Medicine 2000; 57: 588-594.

In this cohort study, 217 workers in a lead battery factory who had had annual blood lead levels measured for each of the 5 preceding years were invited to take a test measure vibration perception threshold (VPT). The study found that five parameters of exposure to lead were all significantly correlated with VPT of the feet. Above a threshold estimated at a median blood lead level of 31 µg/dL, the study found a dose-response relationship between increased blood lead level and increased VPT.

Cross-sectional Studies

Baloh RW, Spivey GH, Brown CP, et al. Subclinical effects of chronic increased lead absorption: A prospective study. II. Results of baseline neurologic testing. Journal of Occupational Medicine 1979; 21: 490-496.

This cross-sectional study found that decreased deep tendon reflexes occurred more frequently in secondary lead smelter workers than in controls (22% vs. 11%; $P = 0.06$).

Chia SE, Chia HP, Ong CN, Jeyaratnam J. Cumulative blood lead levels and nerve conduction parameters. Occupational Medicine 1996; 46: 59-64.

This cross-sectional study found significant differences between the following parameters of peripheral neuropathy in 72 lead battery manufacturing workers as compared with 82 non-exposed referents: median sensory motor conduction velocity, distal latency, and amplitude.

Kovala T, Matikainen E, Mannelin T, et al. Effects of low level exposure to lead on neurophysiological functions among lead battery workers. Occupational and Environmental Medicine 1997; 54: 487-493.

This cross-sectional study of 60 workers from a lead battery factory found that sensory amplitudes and sensory and motor conduction velocities demonstrated a negative correlation with long-term exposure to lead.

Rubens O, Logina I, Kravale I, et al. Peripheral neuropathy in chronic occupational inorganic lead exposure: A clinical and electrophysiological study. Journal of Neurology, Neurosurgery, and Psychiatry 2001; 71: 200-204.

This cross-sectional study of 46 patients with increased blood and/or urinary lead concentrations demonstrated mild sensory neuropathy.

Schwartz BS, Lee B-K, Lee G-S, et al. Associations of blood lead, dimercaptosuccinic acid-chelatable lead, and tibia lead with neurobehavioral test scores in South Korean lead workers. American Journal of Epidemiology 2001; 153: 453-464.

This cross-sectional study found that lead-exposed workers performed worse than controls in all of the tested domains, including peripheral nervous system, sensory, and strength testing.

Zheng G, Tian L, Liang Y, et al. δ-aminolevulinic acid dehydratase genotype predicts toxic effects of lead on workers' peripheral nervous system. NeuroToxicology 2011; 32: 374-382.

This cross-sectional study found that high blood lead and urinary lead levels were associated with significantly lower sensory and motor conduction velocities in the median, ulnar, and peroneal nerves.

Biologic mechanism:

Lead induces peripheral nerve segmental demyelination in rodent[1] and avian[2] species. The observation of intranuclear inclusions consistent with lead deposition in Schwann cells suggests that extravasated lead in the interstitial fluid causes direct injury to Schwann cells, giving rise to demyelination.[3] Intermediate outcomes (prior to peripheral neuropathy) have been noted with lead exposure. For example, minor changes in distal motor nerve conduction or CMAP amplitudes, a slight slowing of sensory conduction, and a slightly prolonged sensory conduction velocity have all been noted with lead exposure.[4]

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1. Windebank AJ. Specific inhibition of myelination by lead in vitro; comparison with arsenic, thallium, and mercury. Exp Neurol. 1986 Oct;94(1):203-12.

2. Hunter B, Haigh JC. Demyelinating peripheral neuropathy in a guinea hen associated with subacute lead intoxication. Avian Dis. 1978 Apr-Jun;22(2):344-9.

3. Myers RR. Changes in endoneurial fluid pressure, permeability, and peripheral nerve ultrastructure in experimental lead neuropathy. Ann Neurol. 1980 Oct;8(4):392-401.

4. Rubens O, Logina I, Kravale I, et al. Peripheral neuropathy in chronic occupational inorganic lead exposure: A clinical and electrophysiological study. Journal of Neurology, Neurosurgery, and Psychiatry 2001; 71: 200-204.

It is very difficult to conduct analytical epidemiologic studies (cohort or case-control studies) for allergic disorders, such as allergic contact dermatitis. However, the weight of evidence in the medical and scientific literature strongly supports the fact that chromium in coal ash can cause allergic contact dermatitis (skin allergy).

Case and Case Series Reports

Goh CL. An epidemiological comparison between occupational and non-occupational hand eczema. British Journal of Dermatology 1989; 120: 77-82.

This case series of 2,110 patients with eczema attending a contact dermatitis clinic found that 15 (6%) of the occupational hand eczema cases were due to contact allergy to potassium dichromate, and 8 (2%) of the non-occupational hand eczema cases were due to contact allergy to potassium dichromate.

Shah M, Lewis FM, Gawkrodger DJ. Prognosis of occupational hand dermatitis in metalworkers. Contact Dermatitis 1996; 34: 27-30.

This report, based on a questionnaire survey of 64 metalworkers who were patients seen in a contact dermatitis clinic between 1 and 5 years before, identified 8 patients whose patch testing results indicated that chromate was the cause of their hand dermatitis.

Johansen JD, Menné T, Christophersen J, et al. Changes in the pattern of sensitization to common contact allergens in Denmark between 1985-86 and 1997-98, with a special view to the effect of preventive strategies. British Journal of Dermatology 2000; 142: 490-495.

This case series based on patch tests on consecutive eczema patients seen in dermatology clinics found widespread contact allergy to potassium dichromate. In the 1985-1986 period, 3.0% of those tested had contact allergy to potassium dichromate; in the 1997-1998 period, 1.2% had contact allergy to potassium dichromate.

Lockman LE. Case report: Allergic contact dermatitis and new-onset asthma: Chromium exposure during leather tanning. Canadian Family Physician 2002; 48: 1907-1909.

This paper reported on a case of allergic contact dermatitis as well as new-onset asthma in a 41-year-old woman who had been exposed to potassium dichromate, a chemical used in tanning leather, in her work.

Tan S, Nixon R. Allergic contact dermatitis caused by chromium in a mobile phone. Contact Dermatitis 2011; 65: 239-248.

This paper is a case report of a 71-year-old engineering professor who developed allergic contact dermatitis caused by chromium in a mobile phone.

Wong CC, Gamboni SE, Palmer AM, Nixon RL. Occupational allergic contact dermatitis to chromium from cement: Estimating the size of the problem in Australia. Australasian Journal of Dermatology 2015; 56: 290-293.

This paper reported on a case series of 3,685 patients who were patch tested for chromium in an occupational dermatology clinic over 20-year period. The authors estimated that there were at least 24 cases of occupational allergic contact dermatitis due to chromium in cement during that period of time.

Review Articles

Diepgen TL, Coenraads PJ. The epidemiology of occupational contact dermatitis. International Archives of Occupational and Environmental Health 1999; 72: 496-506.

This review article of occupational contact dermatitis found evidence that chromium, in the form of dichromate, was a major cause of allergic contact dermatitis in several occupational groups, including construction workers, tile setters, electroplaters, leather workers, and metalworkers.

Shelnutt SR, Goad P, Belsito DV. Dermatological toxicity of hexavalent chromium. Critical Reviews in Toxicology 2007; 37: 375-387.

This paper reviews the etiology, prevalence, pathology, dose-response, and prognosis of both allergic contact dermatitis and skin ulcers due to exposure to hexavalent chromium. This publication cites reports in the literature that indicate that repeated exposure to hexavalent chromium can induce both sensitization and elicit allergic contact dermatitis due to chromium. This paper cites data to support a dose-response relationship. The authors comment that allergic contact dermatitis due to chromium can be a chronic debilitating disease, possibly because chromium is ubiquitous in foods and in the environment and is difficult to avoid.

Bregnbak D, Johansen JD, Jellesen MS, et al. Chromium allergy and dermatitis: Prevalence and main findings. Contact Dermatitis 2015; 73: 261-280.

This review article states that, although published studies have shown mainly positive associations between chromium exposure and atopic dermatitis, these findings could be attributable to false-positive test reactions that may have occurred due to the irritating properties of a chromium patch test preparation.

Nickel and Allergic Contact Dermatitis (Skin Allergy)

It is very difficult to conduct analytical epidemiologic studies (cohort or case-control studies) for allergic disorders, such as allergic contact dermatitis. However, the weight of evidence in the medical and scientific literature strongly supports the fact that nickel in coal ash can cause allergic contact dermatitis (skin allergy).

Cross-sectional Study

Mattila L, Kilpeläinen M, Terho EO, et al. Prevalence of nickel allergy among Finnish university students in 1995; Contact Dermatitis 2001; 44: 218-223.

This cross-sectional study of first-year university students found nickel allergy in 42% of females and 3% of males tested. The authors found that skin piercing and current metal contacts were important risk factors for nickel allergy.

Case and Case Series Reports

Goh CL. An epidemiological comparison between occupational and non-occupational hand eczema. British Journal of Dermatology 1989; 120: 77-82.

This case series of 2,110 patients with eczema attending a contact dermatitis clinic found that 23 (8%) of the occupational hand eczema cases were due to contact allergy to nickel sulfate, and 67 (13%) of the non-occupational hand eczema cases were due to contact allergy to nickel sulfate.

Shah M, Lewis FM, Gawkrodger DJ. Prognosis of occupational hand dermatitis in metalworkers. Contact Dermatitis 1996; 34: 27-30.

This report, based on a questionnaire survey of 64 metalworkers who were patients seen in a contact dermatitis clinic between 1 and 5 years before, identified 7 patients whose patch testing results indicated that nickel was the cause of their hand dermatitis.

Johansen JD, Menné T, Christophersen J, et al. Changes in the pattern of sensitization to common contact allergens in Denmark between 1985-86 and 1997-98, with a special view to the effect of preventive strategies. British Journal of Dermatology 2000; 142: 490-495.

This case series based on patch tests on consecutive eczema patients seen in dermatology clinics found widespread sensitization to nickel. Nickel was the most common contact
allergen found, both in the 1985-1986 period (4.2% in men and 18.3% in women) and the 1997-1998 period (4.9% in men and 20.0% in women).

Review Articles

Barceloux DG. Nickel. Clinical Toxicology 1999; 37: 329-258.

This review article on nickel stated that nickel is the most common sensitizing metal, with a high prevalence rate (29%) in a study of patients attending an allergy clinic. The paper stated that, once sensitization occurs, hypersensitivity to nickel usually lasts indefinitely.

Diepgen TL, Coenraads PJ. The epidemiology of occupational contact dermatitis. International Archives of Occupational and Environmental Health 1999; 72: 496-506.

This review article of occupational contact dermatitis found evidence that nickel was the leading cause of allergic contact dermatitis among metalworkers and the second most frequent cause of allergic contact dermatitis among hairdressers.

Hostýnek JJ. Nickel-induced hypersensitivity: Etiology, immune reactions, prevention and therapy. Archives of Dermatological Research 2002; 294: 249-267.

This review article stated that exposure to nickel is among the most frequent causes of hypersensitivity. The paper stated that nickel has been confirmed in epidemiologic studies as the most prevalent contact allergen in the general population in the industrialized world

Chromium and Asthma

It is very difficult to conduct analytical epidemiologic studies (cohort or case-control studies) for allergic disorders, such as asthma. However, the weight of evidence in the medical and scientific literature strongly supports the fact that exposure to chromium in coal ash can cause asthma.

Cross-sectional Studies

Walters GI, Moore VC, Robertson AS, et al. An outbreak of occupational asthma due to chromium and cobalt. Occupational Medicine 2012; 62: 533-540.

This cross-sectional study of 62 workers who were exposed to both chromium and cobalt found that 61% of these workers had high exposure to metalworking fluid. Of these 62 workers, 90% had urinary chromium excretion, indicating occupational exposure. Among all workers, 66% reported active respiratory symptoms. Two additional workers with probable occupational asthma were identified; they had significantly higher urinary chromium and cobalt concentration than asymptomatic controls.

Wittczak T, Dudek W, Walusiak-Skorupa J, et al. Metal-induced asthma and chest x-ray changes in welders. International Journal of Occupational Medicine and Environmental Health 2012; 25: 242-250.

This cross-sectional study identified 9 cases of occupational asthma in welders, 3 of which were due to nickel and 3 of which were due to chromium.

Rosa MJ, Benedetti C, Peli M, et al. Association between personal exposure to ambient metals and respiratory disease in Italian adolescents: A cross-sectional study. BMC Pulmonary Medicine 2016; 16:6 doi.10.1186/s12890-016-0173-9.

This cross-sectional study in adolescents found a significant association between (a) parental reports of asthma in these adolescents, and (b) both nickel (relative risk = 1.11; 95% CI, 1.03-1.21) per 4 ng/m^3 increase and chromium (relative risk = 1.08; 95% CI, 1.06-1.11) per
9 ng/m^3 increase.

Case and Case Series Reports

Keskinen H, Kalliomäki PL, Alanko K. Occupational asthma due to stainless steel welding fumes. Clinical Allergy 1980; 10: 151-159.

This report included five stainless steel welders with occupational asthma caused by fumes from manual metal arc stainless steel welding.

Novey HS, Habib M, Wells ID. Asthma and IgE antibodies induced by chromium and nickel salts. Journal of Allergy and Clinical Immunology 1983; 72: 407-412.

This is a report of a 32-year-old electroplater who was exposed to both chromium and nickel and developed occupational asthma.

Park HS, Yu HJ, Jung KS. Occupational asthma caused by chromium. Clinical and Experimental Allergy 1994; 24: 676-681.
This is a report of 4 cases of occupational asthma caused by chromium salts.

Shirakawa T, Morimoto K. Brief reversible bronchospasm resulting from bichromate exposure. Archives of Environmental Health 1996; 51: 221-226.
This is a report of a 50-year-old worker who developed an asthmatic reaction after exposure to bichromate in a metal-plating plant.

Bright P, Burge PS, O'Hickey SP, et al. Occupational asthma due to chrome and nickel electroplating. Thorax 1997; 52: 28-32.
This is a report of 70 workers who developed occupational asthma after being exposed to chrome and nickel fumes from electroplating.

De Raeve H, Vandecasteele C, Demedts M, Nemery B. Dermal and respiratory sensitization to chromate in a cement floorer. American Journal of Industrial Medicine 1998; 34: 169-176.
This is a report of a 48-year-old floorer who had occupational exposure to cement and developed chromate contact dermatitis as well as occupational asthma due to chromate.

Kolarzyk E, Stepniewski M, Zapolska I. Occurrence of pulmonary diseases in steel mill workers. International Journal of Occupational Medicine and Environmental Health 2000; 13: 103-112.
This is a report of 36 workers with occupational asthma who were steel mill workers.

Sastre J, Fernandez-Nieto M, Maranon F, Fernandez-Caldas E. Allergenic cross-reactivity between nickel and chromium salts in electroplating-induced asthma (Letter to the Editor). Journal of Allergy and Clinical Immunology 2001; 108: 650-651.
This is a report of occupational asthma in a 36-year-old man who worked in a metal plating factory where he was exposed to nickel sulfate and chromium potassium sulfate.

Hannu T, Piipari R, Kasurinen H, et al. Occupational asthma due to manual metal-arc welding of special stainless steels. European Respiratory Journal 2005; 26: 73-739.
This is a report of two cases of occupational asthma caused by manual metal-arc welding on special stainless steels, which have a high chromium content.

Fernández-Nieto M, Quirce S, Carnés J, Sastre J. Occupational asthma due to chromium and nickel salts. International Archives of Occupational and Environmental Health 2006; 79: 483-486.
This is a report of occupational asthma in 4 patients who were exposed to chromium and nickel salts.

Huang X, Xie J, Cui X, et al. Association between concentrations of metals in urine and adult asthma: A case-control study in Wuhan, China. PloS One 2016; 11:e0155818.

This case-control study of 551 adult asthma cases and 551 gender- and age-matched controls found that asthma was significantly associated with urinary chromium concentration (odds ratio = 4.89; 95% CI, 3.04-7.89), after adjusting for other metals and other covariates.

Lockman LE. Case report: Allergic contact dermatitis and new-onset asthma: Chromium exposure during leather tanning. Canadian Family Physician 2002; 48: 1907-1909.

This paper reported on a case of new-onset asthma in a 41-year-old woman who had been exposed to potassium dichromate, a chemical used in tanning leather, in her work. Notable features include:

• asthma first appeared during exposure to a recognized etiologic agent at work, i.e., chromium;
• symptoms included recurrent acute episodes of wheezing and dyspnea;
• a temporal association existed between symptoms and work; and
• there was positive response to either bronchial provocation test or skin tests for allergy toward substances encountered at work.

Review Articles

Fernández-Nieto M, Quirce S, Sastre J. Occupational asthma in industry. Allergologia et Immunopathologia 2006; 34: 212-223.

This review article on occupational asthma in industry stated that asthma can be caused by chrome and nickel salts.

Arrandale VH, Liss GM, Tarlo SM, et al. Occupational contact allergens: Are they also associated with occupational asthma? American Journal of Industrial Medicine 2012; 55: 353-360.

This review article on occupational contact allergens and whether or not they are associated with occupational asthma concluded that occupational asthma can be caused both by nickel sulfate and potassium dichromate.

Analogy: Studies in Children

A statistically non-significant increased risk of asthma exposed to coal ash was observed in two studies of children.[1,2]

Mechanisms:

Several mouse models may shed light on biological mechanisms underlying the association between chromium and asthma. In one experiment,[3] groups of ovalbumin protein (OVA)-primed mice were challenged either with OVA alone, or with a combination of OVA and particulate zinc chromate, and various parameters associated with asthmatic responses were

measured. Co-exposure to particulate Cr(VI) and OVA mediated a mixed form of asthma in which both eosinophils and neutrophils are present in airways, tissue pathology was markedly exacerbated, and airway hyperresponsiveness was significantly increased. An increase in IgE production and eosinophil numbers was also observed in Cr salt-treated mice.[4] In that study, Cr salts caused pulmonary sensitization, as evidenced by the significant increase in the total IgE levels and the augmentation of inflammatory cell influx in and around the airways.

References

1. Sears CG, Zierold KM. Health of Children Living Near Coal Ash. Glob Pediatr Health. 2017; 4: 2333794X17720330.

2. Pfeiffer JA. Coal Ash Exposure and Asthma in Children. (Dissertation) https://ir.library.louisville.edu/etd/2806/

3. Schneider BC, Constant SL, Paterno SR, et al. Exposure to Particulate Hexavalent Chromium Exacerbates Allergic Asthma Pathology. Toxicol Appl Pharmacol 2012; 259:38-44. doi:10.1016/j.taap.2011.12.001.

4. Ban M, Langonné I, Goutet M, et al. Simultaneous analysis of the local and systemic immune responses in mice to chromium and platinum. Toxicology 277 (2010) 29-37.

Fine Particulate Matter and Asthma

Analysis of the following medical and scientific literature supports a causal association between exposure to fine particulate matter in coal ash and occurrence of asthma, based on satisfaction of the following Bradford Hill Principles:

Strength
Consistency
Temporality
Biologic Gradient (Dose-response Relationship)
Biologic Plausibility
Analogy

A positive association between fine particulate matter and asthma has been observed in several epidemiologic studies in different populations using several study designs, and controlling for a wide range of potentially confounding factors. In the cohort studies, exposure was measured prior to the measurement of the outcome (temporality), thus avoiding recall bias. Studies often showed positive dose-response associations. Several studies showed relative risk estimated in the moderate to strong range. Cytotoxicity in a number of conventional tests using animal lung cells (and other tissues) and studies showing silica (which is present in coal ash) increases risk of asthma have been suggested as biologically plausible mechanisms. Based on ample published literature, at least two meta-analyses were performed concluding that there is an association between fine particulate matter and asthma.

Cohort Studies

Koenig JQ, Larson TV, Hanley QS, et al. Pulmonary function changes in children associated with fine particulate matter. Environmental Research 1993; 63: 26-38.

This study was performed on 326 elementary school children (including 24 with asthma) who lived in an area with high particulate concentrations, mainly from residential wood burning. The study found that an increase in particulate air pollution was associated with a decline in pulmonary function in children with asthma.

Dales R, Chen L. Frescura AM, et al. Acute effects of indoor air pollution on forced expiratory volume in 1 s: A panel study of schoolchildren with asthma. European Respiratory Journal 2009; 34: 316-323.

This cohort study followed 182 elementary schoolchildren with physician-diagnosed asthma for 28 consecutive days and also monitored ambient hourly air pollution concentrations during this period of time. The study monitored pulmonary function in these children using forced expiratory volume in 1 second (FEV_1), a standard measure of pulmonary obstruction. The study found a significant inverse association between fine particulate matter and decrease in bedtime FEV_1 ($P = 0.024$).

Patel MM, Hoepner L, Garfinkel R, et al. Ambient metals, elemental carbon, and wheeze and cough in New York City children through 24 months of age. American Journal of Respiratory and Critical Care Medicine 2009; 180: 1107-1113.

This cohort study of young children found that exposure to fine particulate matter was not associated with wheezing or cough.

Jung KH, Torrone D, Lovinsky-Desir S, et al. Short-term exposure to $PM_{2.5}$ and vanadium and changes in asthma gene DNA methylation and lung function decrements among urban children. Respiratory Research 2017; 18: 63. doi:10.1186/s12931-017-0550-9.

This cohort study among urban children found that short-term exposure to fine particulate matter was associated with decrements in the following parameters of lung function: forced expiratory volume in 1 second (FEV_1), FEV_1/forced vital capacity ratio, and forced expiratory flow at 25-75% of forced vital capacity.

Meta-analyses

Fan J, Li S, Fan C, et al. The impact of PM2.5 on asthma emergency department visits: A systematic review and meta-analysis. Environmental Science and Pollution Research 2016; 23: 843-850.

This systematic review and meta-analysis found a significant association between fine particulate matter and emergency department visits for asthma. For each 10 $\mu g/m^3$ increase of fine particulate matter at higher concentrations, the relative risk significantly increased 1.5% (95% CI, 1.2%-1.7%). Children were more susceptible than adults; for children, for each 10 $\mu g/m^3$ increase of fine particulate matter at higher concentrations, the relative risk significantly increased 3.6% (95% CI, 1.8%-5.3%).

Lim H, Kwon H-J, Lim J-A, et al. Short-term effect of fine particulate matter on children's hospital admissions and emergency department visits for asthma: A systematic review and meta-analysis. Journal of Preventive Medicine & Public Health 2016; 49: 205-219.

This systematic review and meta-analysis of 26 time-series and case-crossover design studies found a significant association between fine particulate matter and children's hospital admissions and emergency department visits for asthma. The study found that for each short-term 10 $\mu g/m^3$ increase in fine particulate matter, the relative risk increased to 1.048 (95% CI, 1.028-1.067).

Ecological Studies

Norris G, YoungPong SN, Koenig JQ, et al. An association between fine particles and asthma emergency department visits for children in Seattle. Environmental Health Perspectives 1999; 107: 489-493.

This ecological study found a significant association between emergency department visits for asthma in children and fine particulate matter. The study found that a change

of 11 μg/m^3 in fine particulate matter was associated with a significantly increased relative risk of 1.15 (95% CI, 1.08-1.23).

Winquist A, Kirrane E, Klein M, et al. Joint effects of ambient air pollutants on pediatric asthma emergency department visits in Atlanta, 1998-2004. Epidemiology 2014; 25: 666-673.

This ecological study found that increases in Criteria Air Pollutants, including fine particulate matter, were significantly associated with increases in warm-season pediatric asthma emergency department visits (joint-effect relative risk = 1.13; 95% CI, 1.06-1.21).

Summary:

In a 2009 report,[1] the U.S. EPA concluded that exposure to airborne particulates is likely to cause respiratory harm (e.g. worsened asthma, worsened COPD, inflammation). Particle pollution has not only been linked directly to asthma, but also to increased bronchitic attacks, respiratory symptoms, use of asthma medication, and lower lung function, demonstrating a coherent and consistent pattern of related health effects in a range of epidemiologic studies internationally.[2,3] Furthermore, by analogy, significantly increased asthma risk has been noted in people exposed to volcanic ash.[4]

Biologic mechanisms:

In vitro studies have shown that coal fly ash (CFA)—independent of type of coal combustion, origin or precipitation—exerts cytotoxicity in a number of conventional tests using animal lung cells (and other tissues).[5] Silica present in coal ash may also increase risk of asthma,[5,6] and may do so synergistically with other irritants.[5]

References

1. U.S. Environmental Protection Agency, Integrated Science Assessment for Particulate Matter, December 2009. EPA 600/R-08/139F

2. Bates DV. Health indices of the adverse effects of air pollution: the question of coherence. Environ Res. 1992; 59:336–49.

3. Dockery DW. Health Effects of Particulate Air Pollution. Ann Epidemiol 2009;19(4):257–263. doi:10.1016/j.annepidem.2009.01.018.

4. Shimizu Y, Dobashi K, Hisada T, et al. Acute impact of volcanic ash on asthma symptoms and treatment. Int J Immunopathol Pharmacol. 2007 Apr-Jun;20(2 Suppl 2):9-14.

5. Borm PA. Toxicity and occupational health hazards of Coal fly ash (CFA). A review of data and comparison to coal mine dust. Aim Accup Hyg 1996;41:659-676.

6. Environmental Working Group. Danger in the air: health concerns for silica in outdoor air. September 25, 2014.
https://www.ewg.org/research/sandstorm/health-concerns-silica-outdoor-air#.WuUSLy-ZNcA

Nickel and Asthma

It is very difficult to conduct analytical epidemiologic studies (cohort or case-control studies) for allergic disorders, such as asthma. However, the weight of evidence in the medical and scientific literature strongly supports the fact that exposure to nickel in coal ash can cause asthma.

Cohort Study

Patel MM, Hoepner L, Garfinkel R, et al. Ambient metals, elemental carbon, and wheeze and cough in New York City children through 24 months of age. American Journal of Respiratory and Critical Care Medicine 2009; 180: 1107-1113.

This cohort study of young urban children found that an increase in ambient nickel concentration was significantly associated with wheezing.

Cross-sectional Studies

Wittczak T, Dudek W, Walusiak-Skorupa J, et al. Metal-induced asthma and chest x-ray changes in welders. International Journal of Occupational Medicine and Environmental Health 2012; 25: 242-250.

This cross-sectional study identified 9 cases of occupational asthma in welders, 3 of which were due to nickel and 3 of which were due to chromium.

Rosa MJ, Benedetti C, Peli M, et al. Association between personal exposure to ambient metals and respiratory disease in Italian adolescents: A cross-sectional study. BMC Pulmonary Medicine 2016; 16:6 doi.10.1186/s12890-016-0173-9.

This cross-sectional study in adolescents found a significant association between (a) parental reports of asthma in these adolescents, and (b) both nickel (relative risk = 1.11; 95% CI, 1.03-1.21) per 4 ng/m^3 increase and chromium (relative risk = 1.08; 95% CI, 1.06-1.11) per 9 ng/m^3 increase.

Case and Case Series Reports

McConnell LH, Fink JN, Schlueter DP, Schmidt MG. Asthma caused by nickel sensitivity. Annals of Internal Medicine 1973; 78: 888-890.

This is a report of a 24-year-old man who began work at a nickel metal-plating company and developed occupational asthma, with symptoms of nonproductive cough, chest tightness, and wheezing.

Keskinen H, Kalliomäki PL, Alanko K. Occupational asthma due to stainless steel welding fumes. Clinical Allergy 1980; 10: 151-159.

This report included five stainless steel welders with occupational asthma caused by fumes from manual metal arc stainless steel welding.

Block GT, Yeung M. Asthma induced by nickel. JAMA 1982; 247: 1600-1602.

This is a report of a 60-year-old metal polisher with occupational asthma induced by nickel sulfate.

Malo J-L, Cartier A, Doepner M, et al. Occupational asthma caused by nickel sulfate. Journal of Allergy and Clinical Immunology 1982; 69: 55-59.

This is a report of a 28-year-old man who worked at a metal-plating factory. Three years after nickel sulfate was introduced into the electroplating process, he developed cough, slight dyspnea, and wheezing, which were temporally related to work. He was diagnosed with occupational asthma caused by allergy to nickel sulfate.

Novey HS, Habib M, Wells ID. Asthma and IgE antibodies induced by chromium and nickel salts. Journal of Allergy and Clinical Immunology 1983; 72: 407-412.

This is a report of a 32-year-old electroplater who was exposed to both chromium and nickel and developed occupational asthma.

Bright P, Burge PS, O'Hickey SP, et al. Occupational asthma due to chrome and nickel electroplating. Thorax 1997; 52: 28-32.

This is a report of 70 workers who developed occupational asthma after being exposed to chrome and nickel fumes from electroplating.

Kolarzyk E, Stepniewski M, Zapolska I. Occurrence of pulmonary diseases in steel mill workers. International Journal of Occupational Medicine and Environmental Health 2000; 13: 103-112.

This is a report of 36 workers with occupational asthma who were steel mill workers.

Sastre J, Fernandez-Nieto M, Maranon F, Fernandez-Caldas E. Allergenic cross-reactivity between nickel and chromium salts in electroplating-induced asthma (Letter to the Editor). Journal of Allergy and Clinical Immunology 2001; 108: 650-651.

This is a report of occupational asthma in a 36-year-old man who worked in a metal plating factory where he was exposed to nickel sulfate and chromium potassium sulfate.

Fernández-Nieto M, Quirce S, Carnés J, Sastre J. Occupational asthma due to chromium and nickel salts. International Archives of Occupational and Environmental Health 2006; 79: 483-486.

This is a report of occupational asthma in 4 patients who were exposed to chromium and nickel salts.

Review Articles

Morgan LG, Usher V. Health problems associated nickel refining and use. Annals of Occupational Hygiene 1994; 38: 189-198.

This paper reviewed the adverse health effects associated with nickel refining and use, including nickel-associated asthma.

Fernández-Nieto M, Quirce S, Sastre J. Occupational asthma in industry. Allergologia et Immunopathologia 2006; 34: 212-223.

This review article on occupational asthma in industry stated that asthma can be caused by chrome and nickel salts.

Arrandale VH, Liss GM, Tarlo SM, et al. Occupational contact allergens: Are they also associated with occupational asthma? American Journal of Industrial Medicine 2012; 55: 353-360.

This review article on occupational contact allergens and whether or not they are associated with occupational asthma concluded that occupational asthma can be caused both by nickel sulfate and potassium dichromate.

Vanadium and Asthma

It is very difficult to conduct analytical epidemiologic studies (cohort or case-control studies) for allergic disorders, such as asthma. However, the weight of evidence in the medical and scientific literature strongly supports the fact that exposure to vanadium in coal ash can cause asthma.

Cohort Studies

Woodin MA, Liu Y, Neuberg D, et al. Acute respiratory symptoms in workers exposed to vanadium-rich fuel-oil ash. American Journal of Industrial Medicine 2000; 37: 353-363.

This prospective cohort study of 18 boilermakers who were overhauling an oil-fired boiler (and were exposed to vanadium-rich fuel-oil ash while doing so) and 11 utility worker controls found that the boilermakers experienced more frequent and more severe respiratory symptoms than the utility workers. The study also found that the increased frequency and severity of respiratory symptoms was most significant during boiler work and was associated with increased dose estimates of both lung and nasal vanadium (as well as coarse particulate matter).

Patel MM, Hoepner L, Garfinkel R, et al. Ambient metals, elemental carbon, and wheeze and cough in New York City children through 24 months of age. American Journal of Respiratory and Critical Care Medicine 2009; 180: 1107-1113.

This cohort study of young urban children found that increases in ambient vanadium concentration was significantly associated with wheezing.

Jung KH, Torrone D, Lovinsky-Desir S, et al. Short-term exposure to $PM_{2.5}$ and vanadium and changes in asthma gene DNA methylation and lung function decrements among urban children. Respiratory Research 2017; 18: 63. Doi:10.1186/s12931-017-0550-9.

This cohort study of urban children found that exposure to vanadium was associated with altered DNA methylation of allergic and proinflammatory asthma genes that are implicated in air-pollution-related asthma.

Cross-sectional Study

Levy BS, Hoffman L, Gottsegen S. Boilermakers' bronchitis: Respiratory tract irritation associated with vanadium pentoxide exposure during oil-to-coal conversion of a power plant.

This paper describes an outbreak of respiratory symptoms among workers exposed to vanadium pentoxide during oil-to-coal conversion of a power plant. The most frequent symptoms among workers were productive cough, sore throat, dyspnea on exertion, and chest pain or discomfort. However, on physical examination, wheezing (39%) was the most frequent finding. The pulmonary function test that was most remarkably affected was expiratory flow rate over the middle 50% of forced vital capacity. As the authors stated of this article stated at the time: "The term 'boilermakers' bronchitis' used in the title of this report may be something of a misnomer since the syndrome

described herein may not be limited to inflammation of the bronchi. Indeed, the findings of mild hypoxemia and the frequency of reduced $FEF_{25-75\%}$ levels raise the possibility of an obstructive effect on the small airways." This is consistent with a diagnosis of asthma caused by vanadium pentoxide.

Case Series Report

Irsigler GB, Visser PJ, Spangenberg PAL. Asthma and chemical bronchitis in vanadium plant workers. American Journal of Industrial Medicine 1999; 35: 366-374.

This is a report of 40 workers at a vanadium plant who were investigated with blood counts and serum IgE levels, intracutaneous allergen skin tests, spirometry, and bronchoprovocation testing with histamine inhalation or exercise challenge. Of the 40 workers who were studied, 12 had evidence of bronchial hyperreactivity (BHR) compared with 12 age-matched companion subjects whose BHR was normal. This study provided evidence that inhaled vanadium pentoxide induces BHR and asthma in people previously free of lung disease.

Cadmium and Chronic Obstructive Pulmonary Disease

Analysis of the following medical and scientific literature supports a causal association between exposure to cadmium in coal ash and occurrence of chronic obstructive pulmonary disease, based on satisfaction of the following Bradford Hill Principles:

Strength
Consistency
Temporality
Plausibility

A positive association between cadmium exposure and chronic obstructive pulmonary disease (COPD) has been observed in several epidemiologic studies in different populations using several study designs, and controlling for a wide range of potentially confounding factors. In the cohort study, exposure was measured prior to the measurement of the outcome (temporality), thus avoiding recall bias. Although the number of prospective cohort studies is limited, several if the other types of observational studies used measures of exposure that did not rely selely on participants' recall of exposure. Studies often showed positive dose-response associations. Several studies showed relative risk estimated in the moderate to strong range. Acute inflammatory reaction accompanied by a buildup of free radicals has been suggested as a biologically plausible mechanism. Based on ample published literature, at least two reviews of the literature suggested, albeit tentatively, that there may be an association between cadmium exposure and COPD. Animal experiments also tend to support a positive association.

Cohort Studies

Lampe BJ, Park SK, Robins T, et al. Association between 24-hour urinary cadmium and pulmonary function among community-exposed men: The VA Normative Aging Study. Environmental Health Perspectives 2008; 116: 1226-1230.

This cohort study found data consistent with chronic cadmium exposure being associated with reduced pulmonary function. The study found significant decrements in both forced expiratory volume in 1 second (FEV_1) and in forced vital capacity (FVC).

Case-control Study

Armstrong BG, Kazantzis G. Prostatic cancer and chronic respiratory and renal disease in British cadmium workers: A case control study. British Journal of Industrial Medicine 1985; 42: 540-545.

This case-control study found a significant association between ever high/always low exposure to cadmium and bronchitis and emphysema (odds ratio = 1.80; 95% CI, 1.12-2.89). In addition, the study found a significantly increased risk of bronchitis and emphysema among those workers who had at least 10 years of high exposure to cadmium.

Cross-sectional Study

Oh C-M, Oh I-H, Lee J-K, et al. Blood cadmium levels are associated with a decline in lung function in males. Environmental Research 2014; 132: 119-125.

This cross-sectional study, based on data from the Korean National Health and Nutrition Examination Survey, found, that adjusting for covariates, a higher blood cadmium level (but within the normal range) was associated with chronic obstructive pulmonary disease in males (*P* for trend < 0.001), including those who had never smoked (*P* for trend = 0.008).

Mannino DM, Holguin F, Greves HM, et al. Urinary cadmium levels predict lower lung function in current and former smokers: Data from the Third National Health and Nutrition Examination Survey. Thorax 2004; 59: 194-198.

This study, based on data from the Third National Health and Nutrition Examination Survey (NHANES III), found that higher levels or urinary cadmium were associated with significantly lower forced expiratory volumes in 1 second (FEV_1) in current smokers (-2.06%; 95% CI, -2.86% to 1.26% per 1 log increase in urinary cadmium) and in former smokers (-1.95%; 95% CI, -2.87% to 1.03%), but not in never-smokers.

Feng W. The dose–response association of urinary metals with altered pulmonary function and risks of restrictive and obstructive lung diseases: a population-based study in China BMJ Open 2015;5:e007643. doi:10.1136/bmjopen-2015- 007643

This cross-sectional study found significant association of urinary cadmium on forced vital capacity (FVC) and forced expiratory volumes in 1 s (FEV1) A total of 2,460 community-living Chinese adults from the Wuhan cohort.

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Case and Case Series Reports

Lane RE, Campbell ACP. Fatal emphysema in two men making a copper cadmium alloy. British Journal of Industrial Medicine 1954; 11: 118-122.

This is a case report of two men who were producing a copper cadmium alloy who developed fatal emphysema.

Morgan JM, Burch HB, Watkins JB. Tissue cadmium and zinc content in emphysema and bronchogenic carcinoma. Journal of Chronic Diseases 1971; 24: 107-110.

This is a report of tissue metal content in a series of postmortem examinations. Among the 26 examinations of deceased individuals with definite postmortem evidence of emphysema (with bronchitis in almost all of these cases), there was significantly increased average cadmium content in liver.

Leduc D, de Francquen P, Jacobovitz D, et al. Association of cadmium exposure with rapidly progressive emphysema in a smoker. Thorax 1993; 48: 570-571.

This is a report of a case of rapidly progressive emphysema in a 50-year-old man who had smoked a pack of cigarettes a day since the age of 16 and who had worked for 4 years as a furnace worker in a plant producing cadmium salts and oxides, where airborne cadmium levels were demonstrated to be elevated.

Review Articles

Hendrick DJ. Occupation and chronic obstructive pulmonary disease (COPD). Thorax 1996; 51: 947-955.

This review article stated that cadmium appears to cause chronic obstructive pulmonary disease by causing emphysema. The article stated: "Although cadmium is a trace component of cigarette smoke, cumulative exposures from smoking alone are not likely to approach those sustained occupationally. It seems improbable therefore that smoking induced emphysema could be attributed to cadmium."

Cullinan P. Occupation and chronic obstructive pulmonary disease (COPD). British Medical Bulletin 2012; 104: 143-161.

This review article stated: "There is good evidence for an increased risk of COPD from certain specific exposures [including cadmium fume]."

Animal Experiments:

Animal studies also support a link between cadmium exposure and reduced pulmonary function. For example, cadmium inhalation produced pulmonary inflammatory responses in mammals.[1] Daily doses of 1.6 mg/m^3 cadmium aerosol over a 2-week period had increased leukocyte concentrations and alveolar thickening in the lung, and over a 6-week period was associated with acute pulmonary damage and emphysema in rats.[2] The authors concluded that cadmium exposure can lead to an acute inflammatory reaction accompanied by a buildup of free radicals, which can consequently lead to lung inflammation. Thus, in animals, cadmium is associated with physiological changes indicative of reduced pulmonary function consistent with the development of COPD.

References

1. Kirschvink N, Martin N, Fievez L, et al. Airway inflammation in cadmium-exposed rats is associated with pulmonary oxidative stress and emphysema. Free Radic Res 2006;40:241-250.

2. Hart BA. Cellular and biochemical response of the rat lung to repeated inhalation of cadmium. Toxicol Appl Pharmacol 1986;82:281–291.

Fine Particulate Matter
and Chronic Obstructive Pulmonary Disease

Analysis of the following medical and scientific literature supports a causal association between exposure to fine particulate matter in coal ash and occurrence of chronic obstructive pulmonary disease, based on satisfaction of the following Bradford Hill Principles:

Strength
Consistency
Temporality
Biologic Gradient (Dose-response Relationship)
Plausibility
Coherence

A positive association between fine particular matter exposure and chronic obstructive pulmonary disease (COPD) has been observed in many epidemiologic studies in different populations using several study designs, and controlling for a wide range of potentially confounding factors. In the cohort studies, exposure was measured prior to the measurement of the outcome (temporality), thus avoiding recall bias. Studies often showed positive dose-response associations. Several studies showed relative risk estimated in the moderate to strong range. Dust particles can cause direct epithelial damage, resulting in bronchitis and impaired ciliary clearance. Inflammation leading to fibrosis has been suggested as a biologically plausible mechanism. Based on ample published literature, a systematic review and meta-analysis concluded that short-term exposure to a 10 $\mu g/m^3$ increment of ambient fine particulate matter was associated with increased hospitalizations and mortality for COPD.

Cohort Studies

Kariisa M, Foraker R, Pennell M, et al. Short- and long-term effects of ambient ozone and fine particulate matter on the respiratory health of chronic obstructive pulmonary disease subjects. Archives of Environmental & Occupational Health 2015; 70: 56-62.

This cohort study found that mean fine particulate matter and cumulative fine particulate matter exposure were both significantly associated with decrements in post-bronchodilator forced expiratory volume in 1 second (FEV_1).

Rice MB, Ljungman PL, Wilker EH, et al. Long-term exposure to traffic emissions and fine particulate matter and lung function decline in the Framingham Heart Study. American Journal of Respiratory and Critical Care Medicine 2015; 191: 656-664.

This cohort study based on data from the Framingham Heart Study found a significant association between lung function decline and exposure to fine particulate matter. It found that each 2 $\mu g/m^3$ increase in average of fine particulate matter was associated with a 13.5 ml (95% CI, -26.6 to
–0.3) lower forced expiratory volume in 1 second (FEV_1) and a 2.1 ml per year faster decline in FEV_1 (95% CI, -0.41 to
-0.2).

To T, Zhu J, Larsen K, et al. Progression from asthma to chronic obstructive pulmonary disease: Is air pollution a risk factor? American Journal of Respiratory and Critical Care Medicine 2016; 194: 429-438.

This cohort study found that the adjusted hazard ratio of asthma-chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS) and cumulative exposure to fine particulate matter was significantly increased (adjusted hazard ratio = 2.78; 95% CI, 1.62-4.78).

Pinault LL, Weichenthal S, Crouse DL, et al. Associations between fine particulate matter and mortality in the 2001 Canadian Census Health and Environment Cohort. Environmental Research 2017; 159: 406-415.

This cohort study found that each 10 $\mu g/m^3$ increase of fine particulate matter significantly increased the risk of death from chronic obstructive pulmonary disease (fully adjusted hazard ratio = 1.238; 95% CI, 1.106-1.386).

Pun VC, Kazemparkouhi F, Manjourides J, Suh HH. Long-term $PM_{2.5}$ exposure and respiratory, cancer, and cardiovascular mortality in older US adults. American Journal of Epidemiology 2017; 186: 961-969.

This cohort mortality study found that each 10 $\mu g/m^3$ increase in 12-month moving average of fine particulate matter in the Behavioral Risk Factor Surveillance System-adjusted model significantly increased the risk of death from chronic obstructive pulmonary disease (relative risk = 1.174; 95% CI, 1.139-1.209).

Yin P, Brauer M, Cohen A, et al. Long-term fine particulate matter exposure and nonaccidental and cause-specific mortality in a large national cohort of Chinese men. Environmental Health Perspectives 2017; 125:117002.

This study found a significant increased risk of death from chronic obstructive pulmonary disease for each 10 $\mu g/m^3$ in fine particulate matter (mortality hazard ratio = 1.12; 95% CI, 1.10-1.13).

Guo C, Zhang Z, Lau AKH, et al. Effect of long-term exposure to fine particulate matter on lung function decline and risk of chronic obstructive pulmonary disease in Taiwan: a longitudinal, cohort study. Lancet Planet Health 2018;2: e114–25.

COPD in 285,046 participants from the Taiwan MJ Health Management Institution Cohort was examined in relation to PM2.5 levels determined from a satellite-based spatiotemporal model. Every 5 µg/m. increment in PM2.5 was associated with a decrease of 1.18% for forced vital capacity (FVC), 1.46% for forced expiratory volume in 1 s (FEV1), 1.65% for maximum mid-expiratory flow (MMEF), and 0.21% for FEV1:FVC ratio. The decrease accelerated over time. Compared with the participants exposed to the first quartile of PM2.5, participants exposed to the fourth, third, and second quartiles of PM2.5 had a hazard ratio of 1.23 (95% CI 1.09–1.39), 1.30 (1.16–1.46), and 1.39 (1.24–1.56) for COPD development, respectively.

Mortality Projection Studies

Chowdhury S, Dey S. Cause-specific premature death from ambient $PM_{2.5}$ exposure in India: Estimate adjusted for baseline mortality. Environment International 2016; 91: 283-290.

This analysis of cause-specific premature death from ambient fine particulate matter exposure in India estimated that 54.5% of premature death was attributable to chronic obstructive pulmonary disease.

Jain V, Dey S, Chowdhury S. Ambient $PM_{2.5}$ exposure and premature mortality burden in the holy city Varanasi, India. Environmental Pollution 2017; 226: 182-189.

This analysis of ambient fine particulate matter exposure and premature mortality burden in Varanasi, India, showed that a rapid increase in fine particulate matter in the previous 15 years and high persistence of fine particulate matter levels above the national air quality standard
translated to a burden of approximately 1,900 annual premature deaths (an estimated 33% of all annual premature deaths) due to chronic obstructive pulmonary disease.

Cross Sectional Studies

Lin H, et al. The attributable risk of chronic obstructive pulmonary disease due to ambient fine particulate pollution among older adults. Environment International 2018;113:143–148.

The investigators observed a threshold concentration of 30 μg/m3 in the PM2.5-COPD association, above which there was a linear positive exposure-response association between ambient PM2.5 and COPD. The odds ratio (OR) for each 10 μg/m3 increase in ambient PM2.5 was 1.21(95% CI: 1.13, 1.30). The data indicate that ambient PM2.5 exposure could increase the risk of COPD and account for a substantial fraction of COPD among the study population.

Lamichhane DK. Associations between Ambient Particulate Matter and Nitrogen Dioxide and Chronic Obstructive Pulmonary Diseases in Adults and Effect Modification by Demographic and Lifestyle Factors Int. J. Environ. Res. Public Health 2018, 15, 363; doi:10.3390/ijerph15020363

Associations of lung function and COPD with PM10 or PM2.5 were examined among 1,264 Korean adults. The highest tertiles of PM2.5 (37.1 g/m3) exposure were significantly associated with COPD (highest versus lowest tertile); adjusted odds ratio (OR) = 1.79, 95% CI: 1.02–3.13.

Choi et al. Harmful impact of air pollution on severe acute exacerbation of chronic obstructive pulmonary disease: particulate matter is hazardous. Int J COPD 2018;13:1053-1059.

The incidence rate of severe COPD events was statistically significantly higher during periods of high particulate exposure [RR 1.612, 95% CI, 1.065–2.440, *P*=0.024]. Additionally, the particulate matter levels 3 days before hospitalization were statistically significant [RR 1.003, 95% CI, 1.001–1.005, *P*=0.006].

Meta-analysis

Li M-H, Fan L-C, Mao B, et al. Short-term exposure to ambient fine particulate matter increases hospitalizations and mortality in COPD: A systematic review and meta-analysis. Chest 2016; 149: 447-458.

This systematic review and meta-analysis concluded that short-term exposure to a 10 $\mu g/m^3$ increment of ambient fine particulate matter was associated with increased hospitalizations and mortality for chronic obstructive pulmonary disease (odds ratio = 1.048; 95% CI, 1.007-1.091; *P* = 0.022).

Case-crossover Study

Weichenthal SA, Lavigne E, Evans GJ, et al. Fine particulate matter and emergency room visits for respiratory illness: Effect modification by oxidative potential. American Journal of Respiratory and Critical Care Medicine 2016; 194: 577-586.

This case-crossover study found that 3-day mean fine particulate matter concentrations were consistently associated with emergency room visits for all respiratory illnesses.

Ecological Studies

Kumar N, Liang D, Comellas A, et al. Satellite-based PM concentrations and their application to COPD in Cleveland, OH. Journal of Exposure Science and Environmental Epidemiology 2013; 23: 637-646.

This analysis suggested that the risk of acute exacerbation of chronic obstructive pulmonary disease increases 2.3% with a unit increase in fine particulate matter exposure.

Hwang S-L, Guo S-E, Chi M-C, et al. Association between atmospheric fine particulate matter and hospital admissions for chronic obstructive pulmonary disease in Southwestern Taiwan: A population-based study. International Journal of Environmental Research and Public Health 2016; 13: 366 doi:10.3390/ ijerph13040366.

This ecological study found that increased hospitalizations for chronic obstructive pulmonary disease were significantly associated with fine particulate matter concentrations in both spring and winter with relative risks for every 10 $\mu g/m^3$ increase in fine particulate matter being 1.25 (95% CI, 1.22-1.27) and 1.24 (95% CI, 1.23-1.26), respectively.

Xu Q, Li X, Wang S, et al. Fine particulate air pollution and hospital emergency room visits for respiratory disease in urban areas in Beijing, China, in 2013. Plos One 2016; 11:e0153099.

This ecological study found that fine particulate matter exposure was significantly associated with respiratory emergency room visits especially for upper respiratory tract infection, lower respiratory tract infection, and acute exacerbations of chronic obstructive pulmonary disease. For each 10 $\mu g/m^3$ increase in fine particulate matter

there was a 0.23% increase in total respiratory disease visits (95% CI, 0.11% to 0.34%), a 0.19% increase for upper respiratory tract infections (95% CI, 0.04% to 0.35%), a 0.34% increase for lower respiratory tract infection (95% CI, 0.14% to 0.53%), and a 1.46% increase for acute exacerbation of chronic obstructive pulmonary disease (95% CI, 0.13% to 2.79%).

Chen R, Yin P, Meng X, et al. Fine particulate air pollution and daily mortality: A nationwide analysis in 272 Chinese cities. American Journal of Respiratory and Critical Care Medicine 2017; 196: 73-81.

This ecological study found that each 10 $\mu g/m^3$ increase in 2-day moving average of fine particulate matter concentrations was significantly associated with an increment in mortality of 0.38% from chronic obstructive pulmonary disease.

Hwang S-L, Lin Y-C, Guo S-E, et al. Fine particulate matter on hospital admissions for acute exacerbation of chronic obstructive pulmonary disease in southwestern Taiwan during 2006-2012. International Journal of Environmental Health Research 2017; 27: 95-105.

This ecological study found that increased hospital admissions for acute exacerbations of chronic obstructive pulmonary disease was significantly associated with ambient particulate matter level. For every 10 $\mu g/m^3$ increase in fine particulate matter during the cold season, there was a significant increase in admissions for exacerbation of chronic obstructive pulmonary disease (relative risk = 1.02; 95% CI, 1.007-1.040).

Lo W-C, Shie R-H, Chan C-C, Lin H-H. Burden of disease attributable to ambient fine particulate matter exposure in Taiwan. Journal of the Formosan Medical Association 2017; 116: 32-40.

This analysis estimated that in 2014 in Taiwan fine particulate matter accounted for 645 deaths due to chronic obstructive pulmonary disease (95% CI, 418-872). The population attributable risk for ambient fine particulate matter was 18.6% (95% CI, 16.9% to 20.3%) for deaths due to ischemic heart disease, stroke, lung cancer, and COPD combined.

Song C, He J, Wu L, et al. Health burden attributable to ambient $PM_{2.5}$ in China. Environmental Pollution 2017; 223: 575-586.

This ecological study found data suggesting that ambient fine particulate matter in 2015 in China contributed to as much as 18.7% of deaths due to chronic obstructive pulmonary disease.

Wang Q, Wang J, He MZ, et al. A county-level estimate of $PM_{2.5}$ related chronic mortality risk in China based on multi-model exposure data. Environment International 2018; 110: 105-112.

This ecological study estimated that premature deaths attributed to fine particulate matter nationwide in China amounted to 1.27 million, with 119,167 of these due to adult chronic obstructive pulmonary disease. Premature deaths from respiratory disease were predominantly in counties with high average ambient fine particulate matter concentrations.

Case Report:

Cho K. Acute Lung Disease After Exposure to Fly Ash [Case Report]. Chest 1994; 106:309-11.

Biologic mechanisms:

As described by Seaman,[1] when dust is inhaled, the larger particulates deposit on the mucosa of the nose and large airways and are cleared by mucociliary transport in approximately 8 hours. Smaller particles reach the alveoli and are phagocytized by alveolar macrophages. Macrophages migrate to the lymphatics where they are eliminated. Lymphatic drainage is driven by pulmonary artery pressure (lower in the apices and on the right) and chest wall excursion (lowest in the upper posterior chest wall). The slowest lymphatic clearance and thus greatest retention of particles is in the upper posterior lung, right worse than left. A high particulate burden rapidly overwhelms these mechanisms. Macrophage aggregates may be engulfed by type I pneumocytes and incorporated into the interstitium. Dust particles can cause direct epithelial damage, resulting in bronchitis and impaired ciliary clearance. Alveolar macrophages release inflammatory mediators that produce extracellular matrix components, such as collagen, and stimulate fibroblasts leading to fibrosis. Recruitment of peripheral blood monocytes and neutrophils causes alveolar inflammation and damage to the alveolar epithelial cells. Damage to the airspaces can result in emphysema. Mineral dust exposure is a complex interaction of reactive oxygen species, antioxidants, cytokines, growth factors, eicosanoids, proteases, and antiproteases, thus leading to lung damage. Due to the relatively large surface area, PM2.5 can absorb large amounts of toxic substances. Due to their small size, PM2.5 can be inhaled and deposited in the alveolar and can aggravate airway inflammation and immune response that can induce COPD.[2] Specific mechanisms have been investigated in several animal experiments. For example, inhaled PM2.5 promoted the overactivation of the Notch signaling pathway and aggravated COPD.[3] Another experiment found that PM2.5 works through the Shh signaling pathway to promote the migration of human bronchial smooth muscle cells, and hence a possible role for PM2.5 in airway remodeling in COPD.[5] Silica, which is present in coal ash and exerts pro-inflammatory effects, has also been linked to COPD.[6]

References

1. Seaman DM. Occupational and Environmental Lung Disease. Clin Chest Med 2015;36:249-268.

2. Chen L. Effects of 1,25-Dihydroxyvitamin D3 on the Prevention of Chronic Obstructive Pulmonary Disease (COPD) in Rats Exposed to Air Pollutant Particles Less than 2.5 Micrometers in Diameter (PM2.5). Med Sci Monit, 2018; 24: 356-362. DOI: 10.12659/MSM.905509

3. Gu XY, Chu X, Zeng XL, et al. Effects of PM2.5 exposure on the Notch signaling pathway and immune imbalance in chronic obstructive pulmonary disease. Environ Pollut 2017;226:163-173. doi: 10.1016/j.envpol.2017.03.070.

5. Ye X, Hong W, Hao B, et al. PM2.5 promotes human bronchial smooth muscle cell migration via the sonic hedgehog signaling pathway. Respiratory Research 2018;19:37.

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Fine particulate matter and other coal ash constituents and respiratory conditions

It is very difficult to conduct analytical epidemiologic studies (cohort or case-control studies) for general respiratory disorders. However, the weight of evidence in the medical and scientific literature strongly supports the fact that exposure to various constituents in coal ash can cause respiratory conditions, including cough, sore throat, dyspnea on exertion, chest pain or discomfort, bronchitis and emphysema.

Cross-sectional Studies

Schilling CJ, Tams IP, Schilling RSF, et al. A survey into the respiratory effects of prolonged exposure to pulverised fuel ash. British Journal of Industrial Medicine 1988; 45: 810-817.

This survey of 268 men with a history of more than 10 years exposure to pulverized fuel (coal) ash found that men with prolonged heavy exposure had higher prevalence of respiratory symptoms, including cough, chronic phlegm, grade 2 or higher dyspnea, "regular wheeze," and chest tightness. In addition, the study found that prolonged heavy exposure was associated with decreased forced vital capacity, vital capacity, peak flow, and gas transfer.

Nicholas GP, Cragle DL, Benitez JG. Medical screening after a coal fly ash spill in Roane County, Tennessee. Disaster Medicine and Public Health Preparedness 2014; 8: 341-348.

A medical screening program was conducted for 214 community residents who believed that their health may have been affected by a coal fly ash spill at the Tennessee Valley Authority Kingston Fossil Plant in Harriman, Tennessee, on December 22, 2008. The most commonly reported symptoms were related to upper airway irritation, including runny nose, cough, and congestion. Before the spill, symptoms related to head, eyes, ears, nose, and throat (HEENT) were present in 23% of participants and pulmonary symptoms were present in 38%. After the spill, 65% of participants reported HEENT symptoms and 52% reported pulmonary symptoms. Pulmonary function tests were performed on 194 participants, 146 (75%) of whom had normal lung function. Of those with abnormal results, 37% occurred among never-smokers.

Sears CG, Zierold KM. Health of children living near coal ash. Global Pediatric Health 2017; 4: 1-8.

This cross-sectional study included 111 children who lived in a community adjacent to coal ash storage sites. Significantly increased problems included attention-deficit hyperactivity disorder, gastrointestinal problems, difficulty falling asleep, frequent night awakenings, and leg cramps. Asthma occurred more frequently among exposed children in comparison with non-exposed children (26% vs. 18%), but this difference was not statistically significant. The adjusted odds ratio for asthma among exposed children was 2.52 (95% CI, 0.8-7.6).

The study also found a significant increase in reported allergies among children living near coal ash (adjusted odds ratio = 3.96; 95% CI, 1.6-10).

Case Reports

Davison AG, Durham S, Newman Taylor AJ, Schilling CJ. Asthma caused by pulverized fuel ash. British Medical Journal 1986; 292: 1561.

This is a case report of asthma caused by pulverized fuel (coal) ash in a 27-year-old man who had onset of symptoms
9 months after starting work as a plant attendant at a coal-fired power station.

Cho K, Cho YJ, Shrivastava DP, Kapre SS. Acute lung disease after exposure to fly ash. Chest 1994; 106: 309-311.

This is a report of a 48-year-old man who developed acute lung disease after intensive exposure to coal fly ash. An open lung biopsy showed classic silicotic hyaline nodules. The patient improved after being treated with high-dose steroids and antibiotics. In the Discussion section of the paper, it stated that short-term exposure to fly ash may result in irritation to eyes, skin, or the mucous membrane of the respiratory tract, and that persistent airborne dust exposure may cause chronic bronchitis and pulmonary fibrosis.

Levy BS, Hoffman L, Gottsegen S. Boilermakers' bronchitis: Respiratory tract irritation associated with vanadium pentoxide exposure during oil-to-coal conversion of a power plant.

This paper describes an outbreak of respiratory symptoms among workers exposed to vanadium pentoxide during oil-to-coal conversion of a power plant. The most frequent symptoms among workers were productive cough, sore throat, dyspnea on exertion, and chest pain or discomfort. However, on physical examination, wheezing (39%) was the most frequent finding. The pulmonary function test that was most remarkably affected was expiratory flow rate over the middle 50% of forced vital capacity.

Irsigler GB, Visser PJ, Spangenberg PAL. Asthma and chemical bronchitis in vanadium plant workers. American Journal of Industrial Medicine 1999; 35: 366-374.

This is a report of 40 workers at a vanadium plant who were investigated with blood counts and serum IgE levels, intracutaneous allergen skin tests, spirometry, and bronchoprovocation testing with histamine inhalation or exercise challenge. Of the 40 workers who were studied, 12 had evidence of bronchial hyperreactivity (BHR) compared with 12 age-matched companion subjects whose BHR was normal. This study provided evidence that inhaled vanadium pentoxide induces BHR and asthma in people previously free of lung disease.

Armstrong BG, Kazantzis G. Prostatic cancer and chronic respiratory and renal disease in British cadmium workers: A case control study. British Journal of Industrial Medicine 1985; 42: 540-545.

This case-control study found a significant association between ever high/always low exposure to cadmium and bronchitis and emphysema (odds ratio = 1.80; 95% CI, 1.12-2.89). In addition, the study found a significantly increased risk of bronchitis and emphysema among those workers who had at least 10 years of high exposure to cadmium.

Cho K, Cho YJ, Shrivastava DP, Kapre SS. Acute lung disease after exposure to fly ash. Chest 1994; 106: 309-311.

This is a report of a 48-year-old man who developed acute lung disease after intensive exposure to coal fly ash. An open lung biopsy showed classic silicotic hyaline nodules. The patient improved after being treated with high-dose steroids and antibiotics. In the Discussion section of the paper, it stated that short-term exposure to fly ash may result in irritation to eyes, skin, or the mucous membrane of the respiratory tract, and that persistent airborne dust exposure may cause chronic bronchitis and pulmonary fibrosis.

Literature Review

Dust particles can cause direct epithelial damage, resulting in bronchitis and impaired ciliary clearance. Seaman DM. Occupational and Environmental Lung Disease. Clin Chest Med 2015;36:249-268.)

This article also provides a discussion of potential biological mechanisms. As described by Seaman, when dust is inhaled, the larger particulates deposit on the mucosa of the nose and large airways and are cleared by mucociliary transport in approximately 8 hours. Smaller particles reach the alveoli and are phagocytized by alveolar macrophages. Macrophages migrate to the lymphatics where they are eliminated. Lymphatic drainage is driven by pulmonary artery pressure (lower in the apices and on the right) and chest wall excursion (lowest in the upper posterior chest wall). The slowest lymphatic clearance and thus greatest retention of particles is in the upper posterior lung, right worse than left. A high particulate burden rapidly overwhelms these mechanisms. Macrophage aggregates may be engulfed by type I pneumocytes and incorporated into the interstitium. Dust particles can cause direct epithelial damage, resulting in bronchitis and impaired ciliary clearance. Alveolar macrophages release inflammatory mediators that produce extracellular matrix components, such as collagen, and stimulate fibroblasts leading to fibrosis. Recruitment of peripheral blood monocytes and neutrophils causes alveolar inflammation and damage to the alveolar epithelial cells. Damage to the airspaces can result in emphysema. Mineral dust exposure is a complex interaction of reactive oxygen species, antioxidants, cytokines, growth factors, eicosanoids, proteases, and antiproteases, thus leading to lung damage. Due to the relatively large surface area, PM2.5 can absorb large amounts of toxic substances. Due to their small size, PM2.5 can be inhaled and deposited in the alveolar and can aggravate airway inflammation and immune response that can induce COPD.[1] Specific mechanisms have been investigated in several animal experiments. For example, inhaled PM2.5 promoted the overactivation of the Notch signaling pathway and aggravated COPD.[2] Another experiment found that PM2.5 works through the Shh signaling pathway to promote the migration of human bronchial smooth muscle cells, and hence a possible role for PM2.5 in airway remodeling.

1. Chen L. Effects of 1,25-Dihydroxyvitamin D3 on the Prevention of Chronic Obstructive Pulmonary Disease (COPD) in Rats Exposed to Air Pollutant Particles Less than 2.5 Micrometers in Diameter (PM2.5). Med Sci Monit, 2018; 24: 356-362. DOI: 10.12659/MSM.905509

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Consensus Report:

American Lung Association & Environmental Health & Engineering, Inc. Toxicity and Impacts on Public Health and the Environment. EH&E Report 17505 March 7, 2011.

> This report concluded that hazardous air pollutants emitted to the atmosphere by coal-fired power plants can cause a wide range of adverse health effects including damage to eyes, skin, and breathing passages. This report cited three reports from the U.S. EPA.[1-3] (USEPA, 1998; USEPA, 2011a; USEPA, 2011b).

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